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Iron metabolism

Absorption

- upper small intestine
- about 10% of dietary iron absorbed
- Fe²⁺ (ferrous iron) much better absorbed than Fe³⁺ (ferric iron)
- absorption is regulated according to body's need
- increased by vitamin C, gastric acid
- decreased by proton pump inhibitors, gastric achlorhydria, tetracycline, tannin (found in tea)

Distribution in body:

- total body iron = 4g
- hemoglobin = 70%
- ferritin and haemosiderin = 25%
- myoglobin = 4%
- plasma iron = 0.1%

Transport

- carried in plasma as Fe³⁺ bound to transferrin

Storage

- stored as ferritin in tissues

Excretion

- lost via intestinal tract following desquamation

Iron studies

- 1) Serum iron
- 2) Total iron binding capacity (TIBC)
 - transferrin
 - raised in iron deficiency anaemia (IDA)
 - raised in pregnancy and by oestrogen
- 3) Transferrin saturation:
 - calculated by serum iron / TIBC
- 4) Ferritin:
 - raised in inflammatory disorders
 - low in IDA
- 5) Rarer tests:
 - transferrin receptors increased in IDA

Anaemia of chronic disease

- normochromic/hypochromic, normocytic anaemia
- reduced serum and TIBC
- normal or raised ferritin

Folate metabolism

Drugs which interfere with metabolism

- trimethoprim
- methotrexate
- pyrimethamine

Drugs which can reduce absorption

- phenytoin

Methaemoglobinaemia

- Methaemoglobinaemia describes hemoglobin which has been oxidized from Fe²⁺ (ferrous iron) to Fe³⁺ (ferric iron).
- This is normally regulated by **NADH methaemoglobin reductase**, which transfers electrons from NADH to methaemoglobin resulting in the reduction of methaemoglobin to hemoglobin.
- There is **tissue hypoxia** as Fe³⁺ cannot bind oxygen, and hence the oxidation dissociation curve is moved to the left

Congenital causes

- 1) hemoglobin chain variants: HbM, HbH
- 2) NADH methaemoglobin reductase deficiency

Acquired causes

- 1) drugs:
 1. sulphonamides,
 2. nitrates, sodium nitroprusside,
 3. primaquine
 4. dapsone
 5. Phenacetin
 6. Lidocaine
 7. Procaine
 8. Benzocaine.
- 2) chemicals: aniline dyes

Features:

- 1) dyspnoea, anxiety, headache
- 2) **'chocolate' cyanosis**
- 3) severe: acidosis, arrhythmias, seizures, coma
- 4) normal pO₂ but decreased oxygen saturation

Management:

- 1) NADH - methaemoglobin reductase deficiency: **ascorbic acid**
- 2) if acquired: **IV methylene blue**
- 3) hyperbaric O₂, RBCS Tx, Exchange transfusion or dialysis

- In methaemoglobinaemia, an abnormally large proportion of the iron in haem is oxidized to the ferric state leading to impaired oxygen transport and anemic hypoxia.
- Patients appear to be cyanosed, though the cyanosis does not clear when oxygen is administered.

Clinical features depend on the MetHb levels in blood:

- 1) **The discoloration** of blood and appearance of **cyanosis** manifests when the MetHb levels reach **15-20%**.
- 2) Levels between **20-45%** are associated with **dyspnoea, lethargy, dizziness** and **headaches**.
- 3) MetHb levels **> 45%** is usually associated with **impaired consciousness** and
- 4) Levels above **> 55%** can cause **seizures, coma** and cardiac **arrhythmias**.
- 5) **The lethal concentration** for adults is considered to be more than **> 70%**.

- ☒ Assessments of oxygenation give conflicting results.
- ☒ Standard pulse oximeters give spuriously low readings in the presence of excess methaemoglobin. The patient's cyanosis is therefore attributed to hypoxia.
- ☒ Similarly, oxygen saturations measured by blood gas analyzers will also be low and are accompanied by a **high PaO₂**.

The treatment of choice in acquired methaemoglobinaemia is

⇒ a **1% solution of methylene blue**

Additional treatments which may need to be instituted consist of

- 1) Hyperbaric oxygen therapy
- 2) Exchange transfusion
- 3) Transfusion of RBCs
- 4) Dialysis, and
- 5) The administration of ascorbic acid for patients with G6PD deficiency.

- =====
- Deposition of iron in secondary haemochromatosis (haemosiderosis) is detrimental to tissue function.
 - Oral iron chelators, most notably **deferasirox**, have revolutionized the treatment of this complication of repeated transfusions for chronic anaemia conditions.
 - Desferrioxamine results in compliance issues due to the subcutaneous route and long infusion time, and
 - deferiprone is considered a second-line agent.
 - Deferiprone has been approved as second line in view of its side effect profile, including bloody dyscrasias and liver dysfunction.

Sideroblastic anemia

- A condition where RBCs fail to completely form haem, whose biosynthesis takes place partly in the mitochondrion.
- This leads to **deposits of iron** in the mitochondria that form a ring around the nucleus called a **sideroblast ring**.
- It may be congenital or acquired

A) **Congenital cause:** delta-aminolevulinate synthase-2 deficiency

B) **Acquired causes**

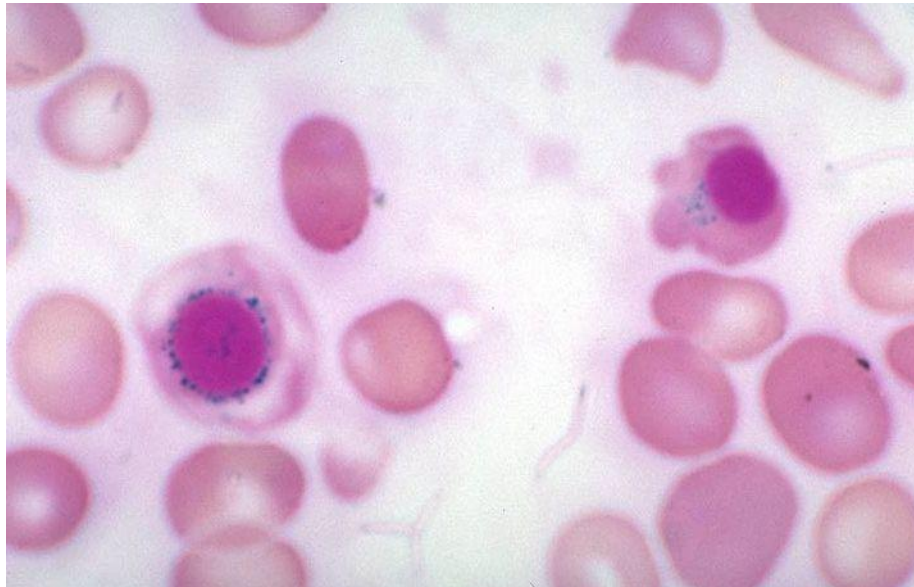
- 1) myelodysplasia
- 2) alcohol
- 3) lead
- 4) anti-TB medications

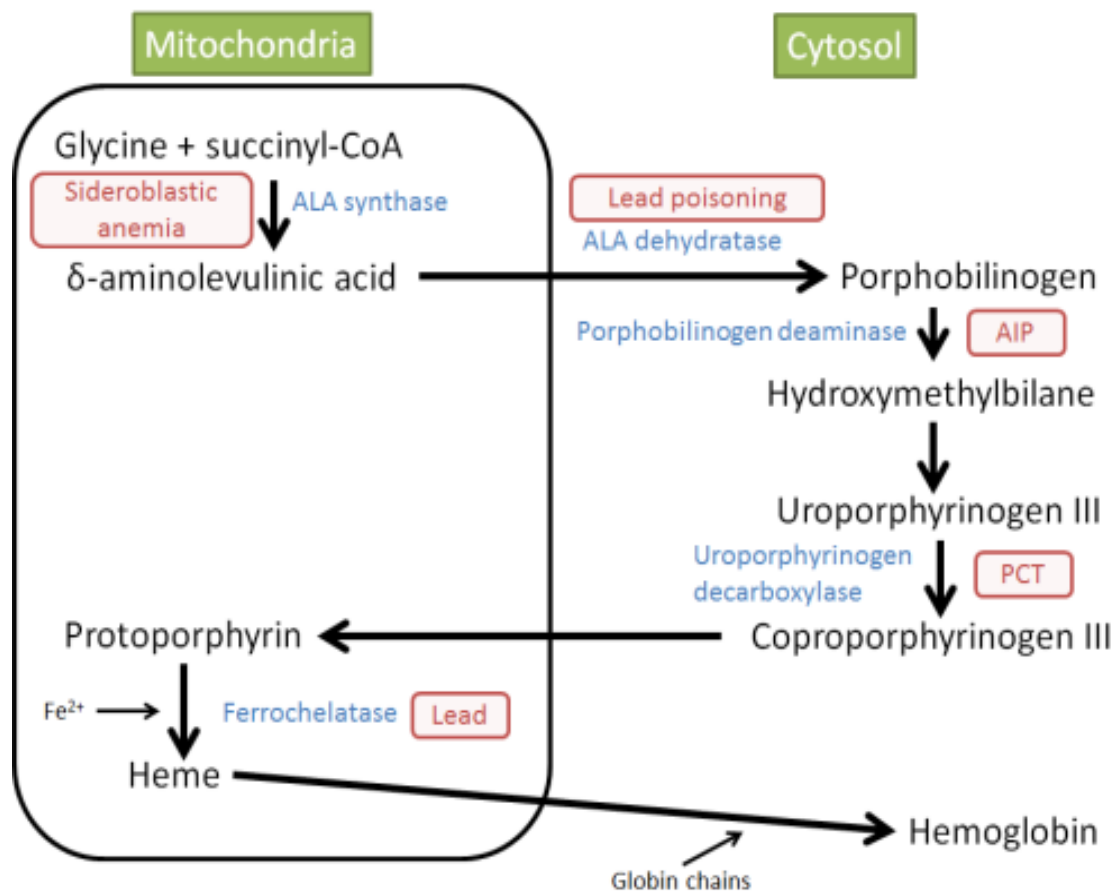
Investigations:

- 1) hypochromic microcytic anemia (more so in congenital)
- 2) bone marrow: **sideroblasts** and **increased iron stores**

Management:

- 1) supportive
- 2) treat any underlying cause
- 3) **pyridoxine** may help





Porphyrias

- Abnormality in enzymes responsible for the biosynthesis of haem
- Results in overproduction of intermediate compounds (porphyrins)
- May be acute or non-acute

Acute intermittent porphyria

- A rare **autosomal dominant** condition
- Caused by a defect in **porphobilinogen deaminase**, an enzyme involved in the biosynthesis of haem.
- This results in the toxic accumulation of **delta aminolaevulinic acid** and **porphobilinogen**.
- It characteristically presents with abdominal and neuropsychiatric symptoms in 20-40 yrs old
- AIP is more common in females (5:1)

Features:

- 1) abdominal: **abdominal pain**, vomiting
- 2) neurological: **motor neuropathy**
- 3) psychiatric: e.g. **depression**
- 4) HTN and tachycardia are common

Diagnosis:

- 1) classically urine turns **deep red on standing**
- 2) raised **urinary porphobilinogen**
(Elevated between attacks and to a greater extent during acute attacks)
- 3) assay of red cells for **porphobilinogen deaminase**
- 4) raised serum **delta aminolaevulinic acid** and **porphobilinogen**

Drugs which may precipitate attack:

- 1) barbiturates
- 2) benzodiazepines
- 3) halothane
- 4) alcohol
- 5) oral contraceptive pill
- 6) sulphonamides

Drugs considered safe to use:

- 1) paracetamol, aspirin
- 2) penicillin
- 3) codeine, morphine
- 4) chlorpromazine
- 5) beta-blockers
- 6) metformin

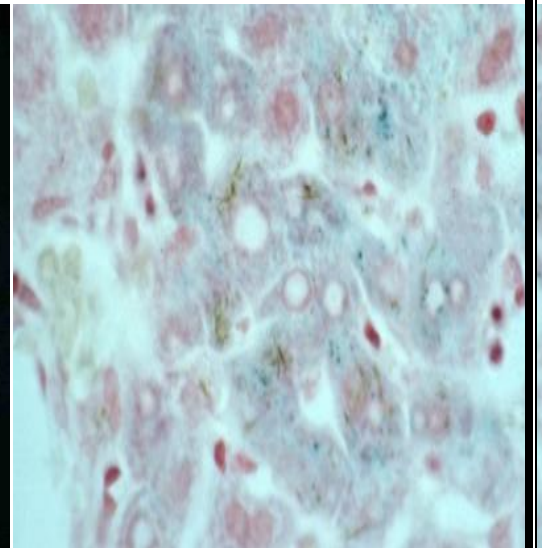
Phenothiazines have antiemetic and antipsychotic properties, making them the medication of choice for acute porphyria episodes. Can be used in migraine

Porphyria cutanea tarda (PCT)

- Most common hepatic porphyria
- Defect in **uroporphyrinogen decarboxylase**
- May be caused by hepatocyte damage e.g. **alcohol**, **oestrogens**, **HCV**

Features:

- 1) Classically **photosensitive rash** with **bullae**,
- 2) **Skin fragility** on face and dorsal aspect of hands,
- 3) Pigmentation,
- 4) **Hypertrichosis**
- 5) Excess alcohol, iron and estrogen are common precipitants.
- 6) The condition may be familial



Liver biopsy

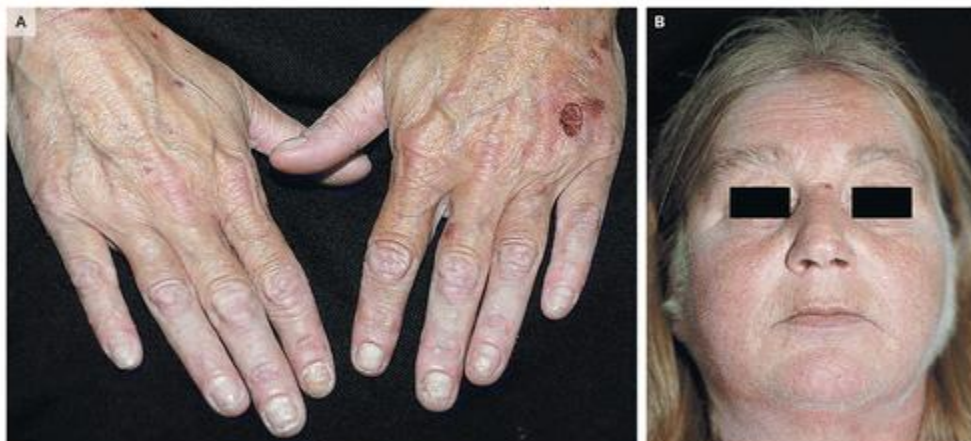
Diagnosis:

Urine:

- ⇒ elevated uroporphyrinogen and
- ⇒ **pink fluorescence** of urine under Wood's lamp

Management:

- 1) **Venesection** is effective (450 ml/week) until hemoglobin is 120 g/L.
- 2) **Chloroquine** may also be effective because it promotes porphyrin excretion.



Patients have excess hair growth (visible in the temporal and malar facial areas in the image)

Variegate porphyria اعراض الاتنين

- Autosomal dominant
- Defect in **protoporphyrinogen oxidase**
- More common in South Africans

Features:

- ⇒ photosensitive blistering rash
- ⇒ abdominal and neurological symptoms

Anaemia
Microcytic anemia
Normocytic anemia
Macrocytic anaemias
Megaloblastic anemia
Macrocytosis without megaloblastic changes

Microcytic anemia

Causes:

- 1) iron-deficiency anemia
- 2) thalassaemia: in beta-thalassaemia minor the microcytosis is often disproportionate to the anemia
- 3) congenital sideroblastic anemia
- 4) lead poisoning
- 5) anemia of chronic disease (more commonly a normocytic, normochromic picture)

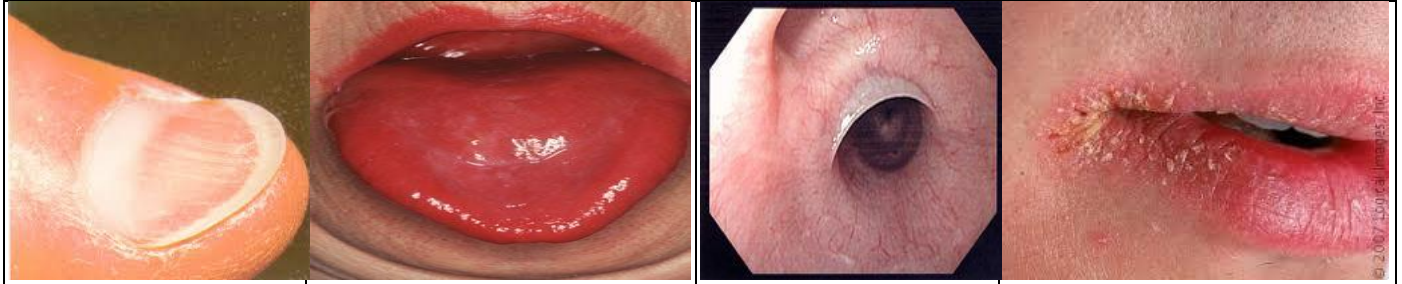
A question sometimes seen in exams gives a history of a normal hemoglobin level associated with a microcytosis:

In patients not at risk of thalassaemia, this should raise the possibility of polycythaemia rubra Vera which may cause an iron-deficiency secondary to bleeding.

Iron deficiency anemia

Features:

- 1) Koilonychia تقعر الأظفار
- 2) Atrophic glossitis
- 3) Post-cricoid webs
- 4) Angular stomatitis



Blood film:

- 1) target cells
 - 2) 'pencil' poikilocytes
 - 3) if combined with B12/folate deficiency a **dimorphic film** occurs with mixed microcytic and macrocytic cells
- ❑ Post-menopausal women and all men with evidence of iron deficiency anaemia require further evaluation and consideration of investigation to exclude **gastrointestinal cancer**.
 - ❑ According to the British Society of Gastroenterology guidance patients with marked anaemia (<120 g/L in men and <100 g/L in women) should be referred urgently as lower levels of haemoglobin reflect more severe disease.

Indications for IV iron include:

- 1) Patients requiring iron supplementation who are unable to tolerate compounds given orally, or
 - 2) Patients with GIT disorders, such as inflammatory bowel disease (ulcerative colitis and Crohn's disease), in which symptoms may be aggravated by oral iron therapy, or
 - 3) Patients who are unable to maintain acceptable iron levels during treatment with hemodialysis
 - 4) Patients who fail to comply with prescriptions for oral iron supplementation.
- It is considered best practice to administer 1000 mg of low molecular weight iron dextran in 250 mL of normal saline in 1 hour without premedication;
 - a test dose of 10 to 25 mg is infused over 3 to 5 minutes prior to the first infusion
 - If no acute reaction is observed, the remaining solution is infused over the balance of 1 hr
 - For those with a history of drug allergies or hypersensitivity, 125 mg of methylprednisolone is infused prior to the test dose.

Although the safety of IV iron has been demonstrated in multiple studies, safety concerns still surround the issue of parenteral iron administration. All iron products can cause hypersensitivity or anaphylaxis, some of which will be severe. The real incidence of adverse events is not known, but one should consider avoiding high molecular weight iron dextran preparations based on published evidence up till now in the literature.

Macrocytic anemia

Macrocytic anemia can be divided into causes associated with a megaloblastic bone marrow and those with a normoblastic bone marrow

Megaloblastic causes	Normoblastic causes
1) vitamin B12 deficiency 2) folate deficiency	1) alcohol 2) liver disease 3) hypothyroidism 4) pregnancy 5) reticulocytosis 6) myelodysplasia 7) drugs: cytotoxics

Pernicious anemia

- a macrocytic anaemia due to B12 deficiency (folate is normal)
- Neurological involvement can be present in B12 deficiency even in the absence of anaemia, especially in patients over the age of 60.
- The peripheral nerves are most commonly involved (peripheral neuropathy), followed by subacute degeneration of the spinal cord. Early signs are loss of peripheral vibration and joint position sense, which is usually followed by loss of reflexes and weakness.
- The legs and feet are usually more involved than the hands.
- In the late stages there may be spasticity, upgoing plantars and ataxia

Investigation:

- 1) **Anti intrinsic factor antibodies** in 50% (**specific for pernicious anemia**)
- 2) **anti gastric parietal cell antibodies** in 85% (but low specificity)
- 3) macrocytic anemia, megaloblasts in marrow
- 4) low WCC and platelets
- 5) **hypersegmented polymorphs** on blood film
- 6) LDH may be raised due to ineffective erythropoiesis
- 7) also low serum B12,
- 8) **Schilling test:**
 - radiolabelled B12 given on two occasions
 - ⇒ first on its own
 - ⇒ second with oral IF(intrinsic factor)
 - urine B12 levels measured

Anti-intrinsic factor antibodies are diagnostic of the condition though may be absent in up to 50% of patients with the condition.

Antigastric parietal cell antibodies are associated with pernicious anaemia and are present in around 85% of cases however they are also found in up to 10% of healthy individuals making them more sensitive but less specific than anti-IF antibodies.

Anaemia due to marrow failure (aplastic anemia)

Aplastic anemia

- Characterised by pancytopenia and a hypoplastic bone marrow
- Peak incidence of acquired = 30 years old

Features:

- 1) Normochromic, normocytic anemia
- 2) Leukopenia, with **lymphocytes relatively spared**
- 3) Thrombocytopenia
- 4) May be the presenting feature acute leukaemia (lymphoblastic or myeloid)
- 5) Minority of patients later develop paroxysmal nocturnal haemoglobinuria or myelodysplasia

Causes:

- 1) idiopathic
- 2) congenital: Fanconi anemia, dyskeratosis congenita
- 3) drugs: cytotoxics, chloramphenicol, sulphonamides, phenytoin, gold
- 4) toxins: benzene
- 5) Parvovirus, hepatitis
- 6) radiation

Management:

- 1) Supportive:
 - ⇒ blood products
 - ⇒ prevention and treatment of infection
- 2) Anti-thymocyte globulin (ATG) and anti-lymphocyte globulin (ALG)
 - ⇒ prepared in animals (e.g. rabbits or horses) by injecting human lymphocytes
 - ⇒ is highly allergenic and may cause serum sickness (fever, rash, arthralgia), therefore steroid cover usually given
- 3) Immunosuppression using agents such as **ciclosporin** may also be given (non myelotoxic)
- 4) Stem cell transplantation:
 - ⇒ **allogeneic transplants** have a success rate of up to 80%

Fanconi anemia

- Autosomal recessive
- Features
 - Aplastic anemia
 - Increased risk of AML
 - Neurological & skeletal abnormalities
 - Skin pigmentation

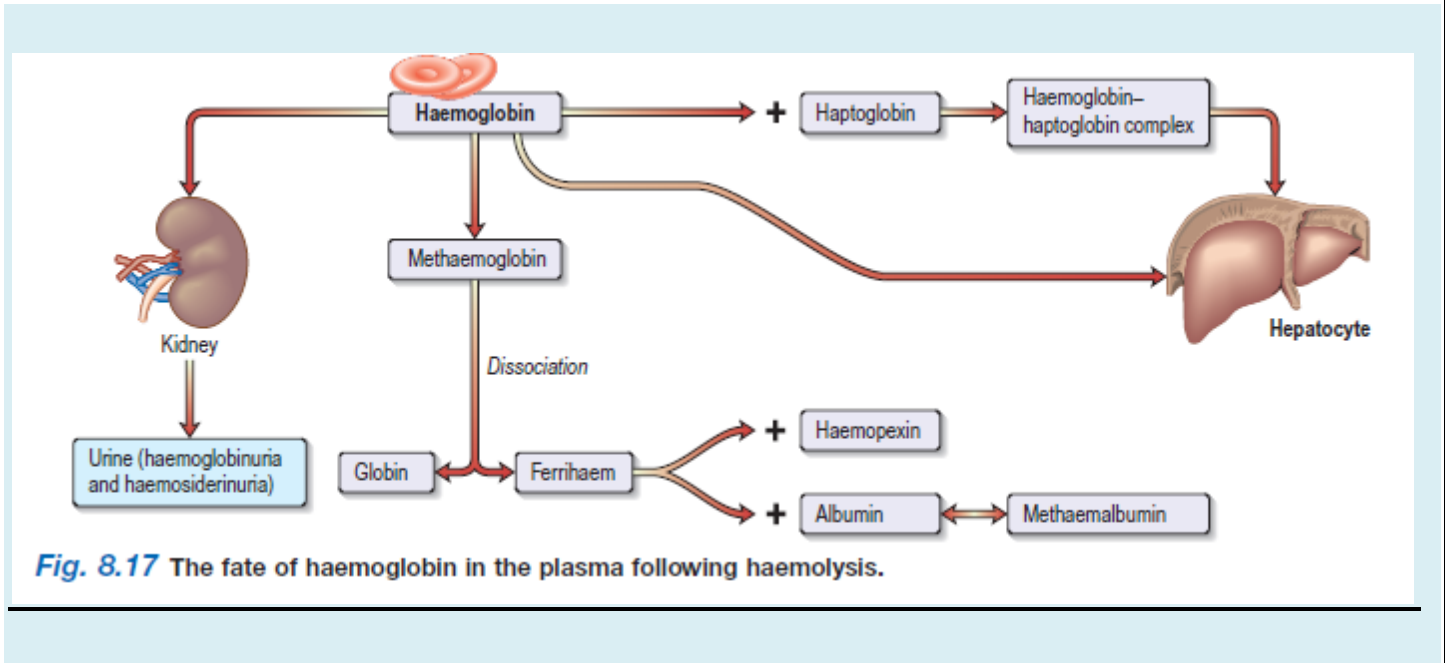
Drug-induced pancytopenia

- 1) Cytotoxics
- 2) Antibiotics: trimethoprim, sulphonamides, chloramphenicol
- 3) Anti-rheumatoid: gold, penicillamine
- 4) Anti thyroid: **carbimazole**: causes both agranulocytosis and pancytopenia
- 5) Anti-epileptics: carbamazepine, phenytoin
- 6) Anti diabetic: sulphonylureas: tolbutamide

Haemolytic anaemias

In intravascular haemolysis:

- Free hemoglobin is released which binds to haptoglobin.
- As haptoglobin becomes saturated, hemoglobin binds to albumin forming methaemalbumin (detected by Schumm's test).
- Free hemoglobin is excreted in the urine as haemoglobinuria, haemosiderinuria



Causes of Intravascular haemolysis:

- 1) mismatched blood transfusion
- 2) G6PD deficiency*
- 3) MicroAngiopathig Heamolytic Anaemia (MAHA)
 - ⇒ red cell fragmentation: heart valves, TTP, DIC, HUS
- 4) paroxysmal nocturnal haemoglobinuria PNH
- 5) cold autoimmune haemolytic anemia cold AIHA

*strictly speaking there is an element of extravascular haemolysis in G6PD as well, although it is usually classified as a intravascular cause

Causes Extravascular haemolysis:

- 1) Haemoglobinopathies: sickle cell, thalassaemia
- 2) Hereditary spherocytosis
- 3) Haemolytic disease of newborn
- 4) Warm autoimmune haemolytic anemia warm AIHA (افتكر الطحال الساخن)

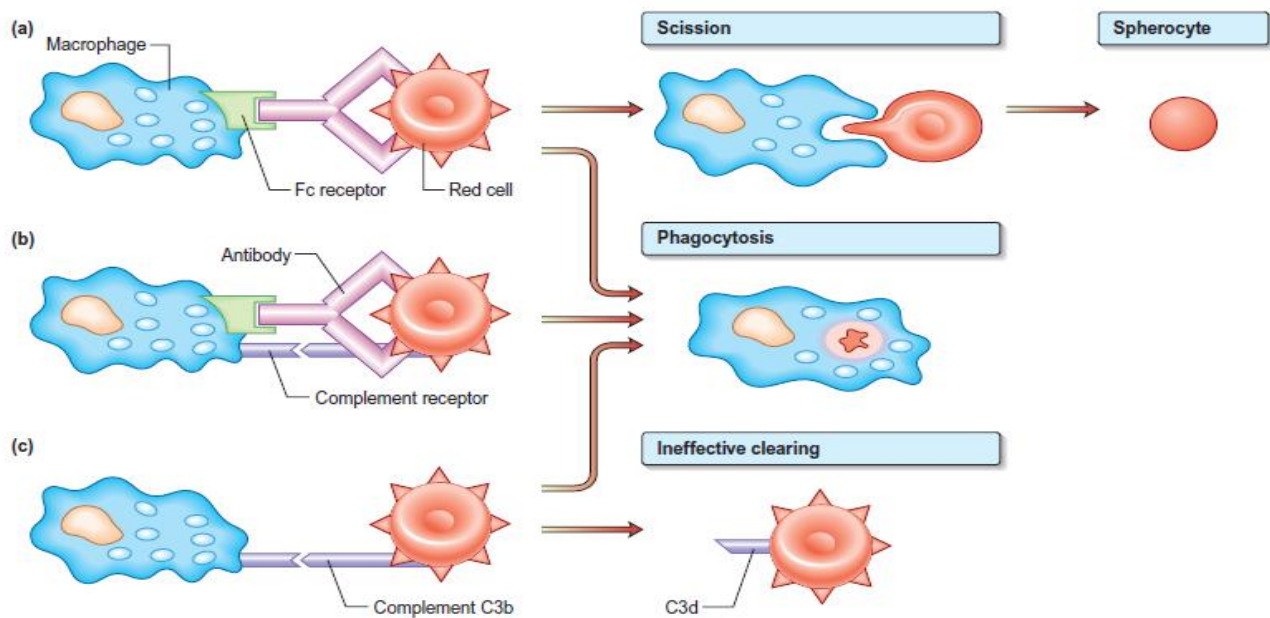


Fig. 8.28 Extravascular haemolysis is due to interaction of antibody-coated cells with cells in the reticuloendothelial system, predominantly in the spleen. (a) Spherocytosis results from partial phagocytosis. (b) Complete phagocytosis may occur and this is enhanced if there is complement as well as antibody on the cell surface. (c) Cells coated with complement only are ineffectively removed and circulate with C3d or C3b on their surface.

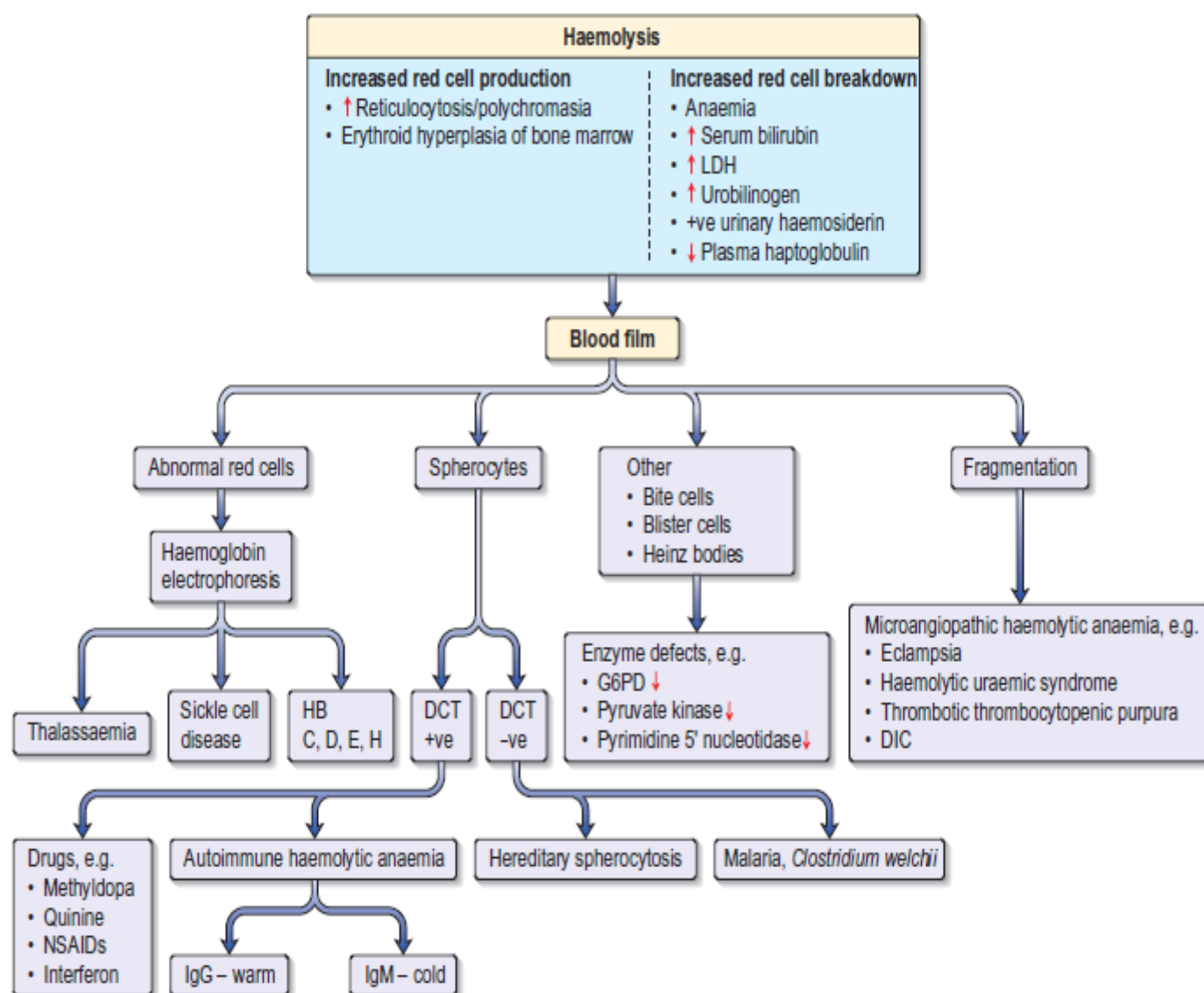


Fig. 8.16 Haemolysis. DCT, direct Coombs' test; G6PD, glucose-6-phosphate dehydrogenase; LDH, lactate dehydrogenase.

Causes of haemolytic anemia

Inherited	Acquired
RBC membrane defect 1) Hereditary spherocytosis 2) Hereditary elliptocytosis Haemoglobinopathy (Hb abnormalities) 1) Thalassaemia 2) Sickle cell disease Metabolic defects 1) G6PD 2) Pyruvate kinase deficiency 3) Pyrimidine kinase deficiency	Immune 1) Autoimmune • Warm • Cold 2) Alloimmune • Haemolytic transfusion reactions • Haemolytic disease of the newborn • After allogeneic BM or organ transplantation 3) Drug-induced Non-immune 1) Acquired membrane defects: A) PNH 2) Mechanical: • MAHA • Valve prosthesis • March haemoglobinuria 3) Secondary to systemic disease - Renal and liver failure Miscellaneous 1) Infections, e.g. ⇒ malaria, ⇒ mycoplasma ⇒ Clostridium welchii, 2) generalized sepsis 3) Drugs and chemicals causing damage to the RBC membrane or oxidative haemolysis 4) Hypersplenism 5) Burns

Red cell membrane defect

1) Hereditary spherocytosis (HS)

2) Hereditary elliptocytosis (HE)

Red cell membrane defects are broadly classified into hereditary spherocytosis, hereditary elliptocytosis.

⇒ Horizontal membrane protein defects (for example, spectrin ankyrin interaction defect) results in **Hereditary elliptocytosis** whereas **autosomal dominant**

⇒ Vertical defects result in **hereditary spherocytosis**

- Elliptocytosis is usually caused by spectrin and spectrin-protein 4.1 defects.
- Heterozygotes are asymptomatic but show elliptocytes on blood film; they do not have haemolysis and do not require any particular treatment

Hereditary spherocytosis

- Most common hereditary haemolytic anemia in people of northern European descent
- **Autosomal dominant** defect of red blood cell cytoskeleton
- The normal biconcave disc shape is replaced by a sphere-shaped red blood cell
- Red blood cell survival reduced as **destroyed by the spleen**

Presentation:

- 1) Failure to thrive
- 2) Jaundice, gallstones, splenomegaly
- 3) Aplastic crisis precipitated by **parvovirus infection**
- 4) Variable degree of haemolysis
- 5) **MCHC elevated**

Diagnosis:

- ☒ **Osmotic fragility test**
- ☒ The osmotic fragility test has now been replaced by the **eosin-5-maleimide** binding to red cells and then being detected by **flow cytometry**.

Management:

- 1) Folate replacement
- 2) Splenectomy

	G6PD deficiency	Hereditary spherocytosis
Gender	Male (X-linked recessive)	Male + female (autosomal dominant)
Ethnicity	African + Mediterranean descent	Northern European descent
Typical history	• Neonatal jaundice • Gallstones • Infection/ drugs precipitate haemolysis • Intravascular Haemolysis	• Neonatal jaundice • Gallstones • Chronic symptoms although haemolytic crises may be precipitated by infection • Splenomegaly is common • Extravascular Haemolysis
Blood film	Heinz bodies	Spherocytes (round, lack of central pallor)
Diagnostic test	enzyme activity of G6PD	Osmotic fragility test

Haemoglobin Abnormalities

- 1) Thalassaemia
- 2) Sickle Cell Disease

Thalassaemia

- The thalassaemias are a group of genetic disorders characterised by a reduced production rate of either alpha or beta chains.

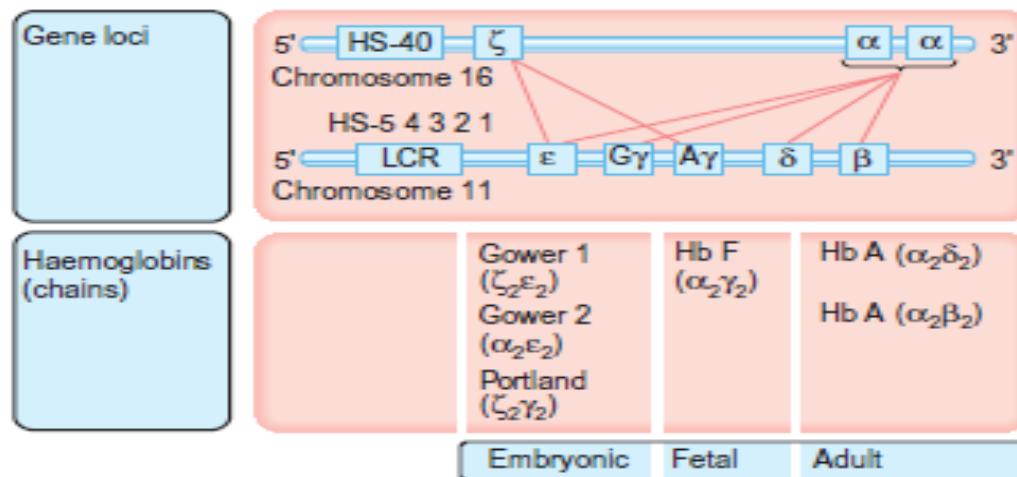


Fig. 8.20 Loci of genes on chromosomes 16 and 11 and the combination of various chains to produce different haemoglobins. HS-40 (for α genes) and locus control region (LCR) HS1–5 (for β genes) are regulatory control elements.

Table 8.10 Some types of haemoglobin

	Haemoglobin	Structure	Comment
Normal	A	$\alpha_2\beta_2$	Comprises 97% of adult haemoglobin
	A ₂	$\alpha_2\delta_2$	Comprises 2% of adult haemoglobin Elevated in β -thalassaemia
	F	$\alpha_2\gamma_2$	Normal haemoglobin in fetus from 3rd to 9th month Increased in β -thalassaemia Comprises < 1% of haemoglobin in adult
Abnormal chain production	H	β_4	Found in α -thalassaemia Biologically useless
	Barts	γ_4	Comprises 100% of haemoglobin in homozygous α -thalassaemia Biologically useless
Abnormal chain structure	S	$\alpha_2\beta_2^S$	Substitution of valine for glutamine acid in position 6 of β chain
	C	$\alpha_2\beta_2^C$	Substitution of lysine for glutamic acid in position 6 of β chain

Alpha-thalassaemia

- due to a deficiency of alpha chains in hemoglobin
- 2 separate alpha-globulin genes are located on each chromosome 16
- Clinical severity depends on the number of alpha chains present

☒ If 1 or 2 alpha chains are absent

- the blood picture would be **hypochromic microcytic**, but
- **the Hb level would be typically normal**

☒ Loss of 3 alpha chains results in

- **Hypochromic microcytic** anemia with **splenomegaly**.
- This is known as **Hb H disease**

☒ If all 4 alpha chains absent (i.e. homozygote) then

- **death in utero** (**hydrops fetalis**, **Bart's hydrops**)

Beta-thalassaemia trait

- Beta-thalassaemia trait is an **autosomal recessive** condition
- Characterised by a **mild hypochromic, microcytic** anemia.
- It is usually **asymptomatic**

Features:

1) Mild microcytic hypochromic anemia:

microcytosis is characteristically disproportionate to the anemia

2) HbA2 raised (> 3.5%) normally it is 2%

Haemoglobin Abnormalities

- 1) Thalassaemia
- 2) Sickle cell disease

Sickle-cell crises

- Sickle cell anemia is characterised by periods of good health with intervening crises
- **Four main types of crises are recognised:**

- 1) thrombotic, 'painful crises'
- 2) sequestration
- 3) aplastic
- 4) haemolytic

A) Thrombotic crises:

- also known as **painful crises** or **vaso-occlusive crises**
- **precipitated by:**
 - 1) infection,
 - 2) dehydration,
 - 3) deoxygenation

Infarcts occur in various organs including:

- 1) the bones e.g. avascular necrosis of hip,
- 2) hand-foot syndrome in children,
- 3) lungs, spleen and brain
- 4) Priapism occurs fairly frequently which may lead to permanent **IMPOTENCE** if it is not relieved

B) Sequestration crises:

- sickling within organs such as the spleen or lungs causes pooling of blood with worsening of the anemia
- **acute chest syndrome:**
 - 1) dyspnoea,
 - 2) chest pain,
 - 3) pulmonary infiltrates,
 - 4) low pO₂
 - 5) the most common cause of death after childhood

C) Aplastic crises:

- caused by infection with **parvovirus**
- sudden fall in hemoglobin

D) Haemolytic crises:

- rare
- fall in hemoglobin due an increased rate of haemolysis

Sickle cell anemia cause nephrogenic Diabetes Insipidus

G6PD deficiency

- The commonest red blood cell enzyme defect
- It is more common in people from the Mediterranean and Africa
- Inherited in a **X-linked recessive** fashion
- Many drugs can precipitate a crisis as well as infections and broad (fava) beans

Pathophysiology:

- ↓ G6PD → ↓ glutathione → increased red cell susceptibility to oxidative stress

Features:

- 1) neonatal jaundice is often seen
- 2) intravascular haemolysis
- 3) gallstones are common
- 4) splenomegaly may be present
- 5) Heinz bodies on blood films

Diagnosis: **G6PD enzyme assay**

Some drugs causing haemolysis:

- 1) anti-malarials: primaquine
- 2) ciprofloxacin
- 3) sulph- group drugs: sulphonamides, sulphasalazine, sulfonyleureas
- 4) Aspirin , quinine & Quinidine

Some drugs thought to be safe

- 1) penicillins, cephalosporins
- 2) macrolides
- 3) tetracyclines
- 4) trimethoprim

Comparing G6PD deficiency to hereditary spherocytosis

	G6PD deficiency	Hereditary spherocytosis
Gender	Male (X-linked recessive)	Male + female (autosomal dominant)
Ethnicity	African + Mediterranean descent	Northern European descent
Typical history	• Neonatal jaundice • Infection/drugs precipitate haemolysis • Gallstones	• Neonatal jaundice • Chronic symptoms although haemolytic crises may be precipitated by infection • Gallstones • Splenomegaly is common
Blood film	Heinz bodies	Spherocytes (round, lack of central pallor)
Diagnostic test	Measure enzyme activity of G6PD	Osmotic fragility test

Acquired haemolytic anemia

Causes of immune destruction of red cells

- ✓ Autoimmune haemolytic anaemias
- ✓ Drug-induced immune haemolytic anemia
- ✓ Alloimmune haemolytic anemia

Causes of non-immune destruction of red cells

- ✓ Acquired membrane defects (e.g. paroxysmal nocturnal haemoglobinuria).
- ✓ Mechanical factors (e.g. prosthetic heart valves, or microangiopathic haemolytic anemia)
- ✓ Secondary to systemic disease (e.g. renal and liver disease).

Autoimmune haemolytic anemia

- Autoimmune haemolytic anemia (AIHA) may be divided in to 'warm' and 'cold' types, according to at what temperature the antibodies best cause haemolysis.
- It is most commonly idiopathic but may be secondary to a lymphoproliferative disorder, infection or drugs.
- AIHA is characterised by a positive direct antiglobulin test (**Coombs' test**)

A) Warm AIHA:

- In warm AIHA the antibody is usually **IgG**
- causes haemolysis best **at body temperature**
- Haemolysis tends to occur in **extravascular** sites, for example **the spleen**. الطحال الساخن
- Management options include **steroids**, **immunosuppression** and **splenectomy**

Causes of warm AIHA

- 1) autoimmune disease: e.g. **SLE**
- 2) neoplasia: e.g. **lymphoma**, **CLL**
- 3) drugs: e.g. **methyldopa**

*SLE can rarely be associated with a mixed-type autoimmune haemolytic anemia

B) Cold AIHA:

- The antibody in cold AIHA is usually **IgM**
- Causes haemolysis best **at 4 deg C**.
- Haemolysis is **mediated by complement** and is more commonly **intravascular**.
- Features may include symptoms of **Raynaud's** and **acrocynosis**.
- Patients **respond less well** to steroids

Causes of cold AIHA:

- 1) neoplasia: e.g. **lymphoma**
- 2) infections: e.g. **mycoplasma**, **Legionella**, **EBV**, **CMV**, **Malaria**

Drug-induced haemolytic anemia:

Can be classified according to 3 different mechanisms:

Type I:

- antibody against **drug-red cell membrane complex**
- **penicillin**

Type II:

- deposition of complement via a **drug-protein-antibody complex** onto red cell membrane
- **quinidine**
- **rifampicin**

Type III:

- true autoimmune haemolytic anemia - role of drug not known
- **methyldopa**
- **L-dopa**
- **mefanamic acid**

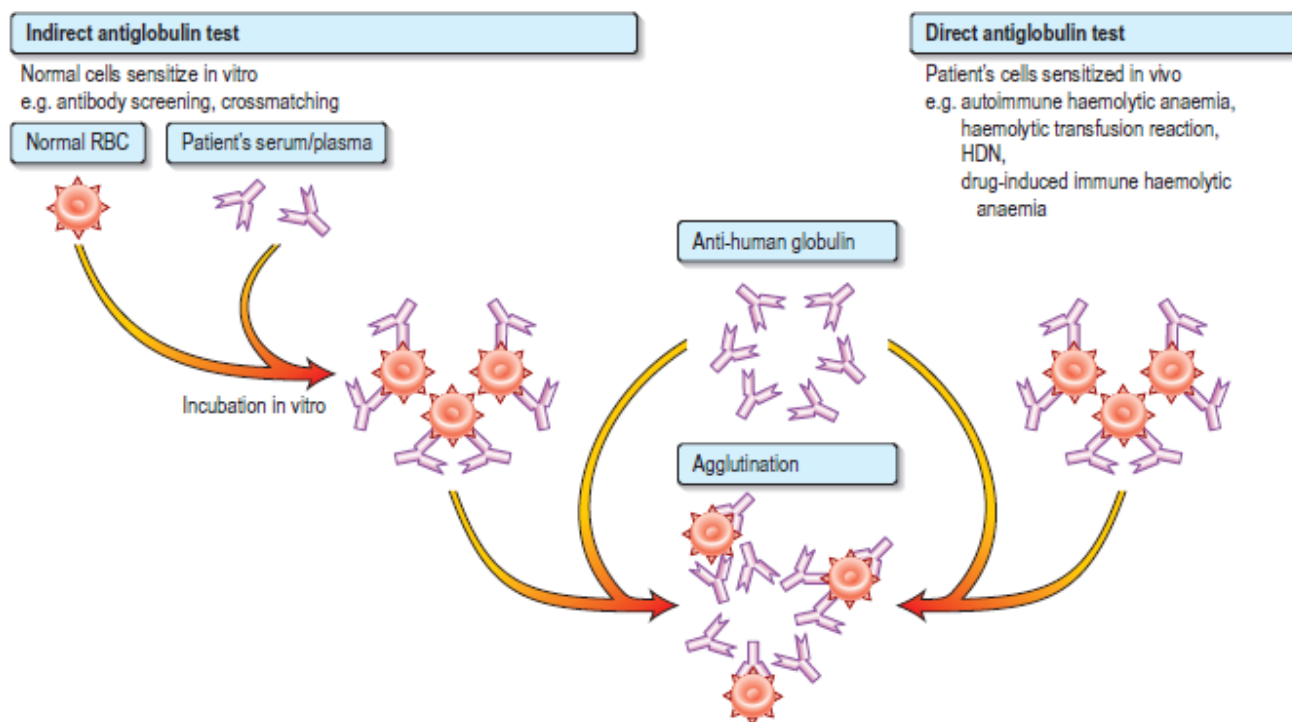


Fig. 8.27 Antiglobulin (Coombs') tests. The anti-human globulin forms bridges between the sensitized cells causing visible agglutination. The direct test detects patients' cells sensitized in vivo. The indirect test detects normal cells sensitized in vitro. HDN, haemolytic disease of newborn.

Paroxysmal nocturnal haemoglobinuria

(PNH)

- An acquired disorder leading to haemolysis (mainly **intravascular**) of haematological cells.
- It is thought to be caused by **increased sensitivity of cell membranes to complement** due to **a lack of glycoprotein glycosyl-phosphatidylinositol (GPI)**.
- Patients are more prone to **venous thrombosis**

Pathophysiology:

- GPI can be thought of as an anchor which attaches surface proteins to the cell membrane
- complement-regulating surface proteins, e.g. decay-accelerating factor (DAF), are not properly bound to the cell membrane due a lack of GPI
- **thrombosis** is thought to be caused by **a lack of CD59 on platelet membranes** predisposing to **platelet aggregation**

Features:

- 1) hemolytic anemia
- 2) **haemoglobinuria**: classically **dark-colored urine in the morning** (although has been shown to occur throughout the day)
- 3) **thrombosis** e.g. **Budd-Chiari syndrome**
- 4) Abdominal pain is common and may be due to **small mesenteric vein thrombi**.
- 5) RBCs, WBCs, platelets or stem cells may be affected therefore **pancytopenia** may be present
- 6) **aplastic anemia** may develop in some patients

Diagnosis:

- 1) **Flow cytometry** of blood to detect low levels of **CD59 and CD55** has now replaced Ham's test as **the gold standard investigation** in PNH
- 2) **Ham's test**: acid-induced haemolysis (normal red cells would not)

Management:

- 1) Blood product replacement
- 2) **Thrombolysis in acute setting & anticoagulation (lifelong)**
- 3) **Eculizumab**: (also used in **HUS**)
 - ☒ a monoclonal antibody **directed against terminal protein C5**,
 - ☒ currently being trialled and is showing promise in reducing intravascular haemolysis
- 4) **Stem cell transplantation**

Blood product transfusion complications

1) Haemolytic reaction:

A) Immediate:

- ⇒ E.g. **ABO mismatch**
- ⇒ massive intravascular haemolysis

B) delayed

2) Febrile reactions:

- ⇒ due to **white blood cell HLA antibodies**
- ⇒ often the result of sensitization by previous pregnancies or transfusions
- ⇒ relieved rapidly on holding transfusion

Immediate-type hypersensitivity reaction: characterised by any combination of urticaria, erythema, maculopapular rash, periorbital oedema, bronchospasm and hypotension.

- ⇒ The appropriate treatment is stopping transfusion, colloids to maintain BP, hydrocortisone, antihistamine, paracetamol and adrenaline where necessary.

3) transmission of viruses, bacteria, parasites

As platelet concentrates are generally stored at room temperature they provide a more favourable environment for bacterial contamination than other blood products.

4) iron overload

5) hyperkalaemia

6) Massive blood tx may cause hypocalcemia

7) ARDS

8) clotting abnormalities

9) DIC: massive blood transfusion > 5 L

10) Causes a degree of immunosuppression

Patients with colorectal cancer who have blood transfusions have a worse outcome than those who do not

- **Leukocyte depleted** blood is already the standard of care in the UK.
- In renal transplant there is an increased risk of graft versus host disease, hence **irradiated blood** is indicated.

Transfusion related acute lung injury (TRALI)

- a severe acute reaction characterised by:
 - ☒ Respiratory distress,
 - ☒ Severe hypoxia,
 - ☒ Fever and
 - ☒ a CXR showing **perihilar and nodular shadowing** in the mid and lower zone, soon after transfusion with no other apparent cause
- In many cases, preformed leucocyte antibodies have been found.
- Cardiogenic causes of pulmonary oedema should be ruled out.
- In contrast to patients with cardiogenic pulmonary oedema, patients with **TRALI** have normal central venous pressure and normal/low pulmonary wedge pressure.

- If patient has been given Rh D positive platelets when she is RhD negative, she will made immune anti-D. It is very often necessary to give D positive platelets to D negative people due to platelet shortage.
- If the recipient of this mismatch is a female of child bearing age then prophylactic anti- D should be administered with the platelets to prevent production of immune anti- D.
- If we did not administer the anti-D. Should she become pregnant in the future, the immune anti-D she has made can cross the placenta and cause haemolytic disease of the fetus/newborn, if the baby is D positive, and this can be life threatening to the baby.
- Therefore any pregnancies would have to be managed by an obstetrician with special interest in fetal medicine and the baby closely monitored and the levels of anti-D in the mother monitored.

Transfusion associated graft versus host disease **(TA-GVHD)**

- A rare but usually fatal complication seen post bone marrow transplantation (BMT)
- It is due to donor lymphocytes in transfused cellular components, for example, blood, platelets.
- These donor lymphocytes recognise the recipient as foreign, and as the recipient is immunocompromised due to the recent BMT they cannot set up a reaction to destroy these incoming lymphocytes.
- In this case the recipient is the host and the incoming lymphocytes are the graft.
- The lymphocytes cause **bone marrow failure**, **liver dysfunction** and **gastrointestinal symptoms**.
- There is no cure, only preventative measures, in that all cellular blood components given to BMT recipients need to be **irradiated**, this limits the functional activity of the lymphocytes.
- It usually occurs about **14 days** after the affected transfusion.

Guidelines for the blood products transfusion:

- Replacement by red cell concentrate once haematocrit falls below 0.30
- Replacement by platelet transfusion once platelets fall below $50 \times 10^9/L$ in bleeding patients and $< 10 \times 10^9/L$ in most other patients
- Cryoprecipitate when fibrinogen falls below 1.0 g/L
- Fresh frozen plasma when PT and/or APTT more than 1.5 times the controls.

Graft versus host disease

- Organs usually involved in GVHD are skin, liver and gut.
- The rash on the palms and soles (diffuse macular rash)
- Abnormal liver function tests (LFTs)
- Diarrhea.
- The full blood count (FBC) is normal

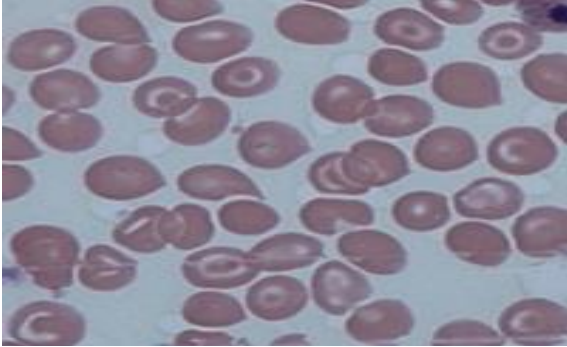
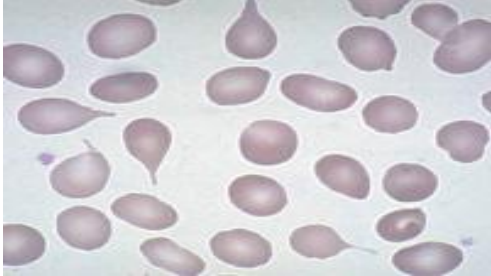
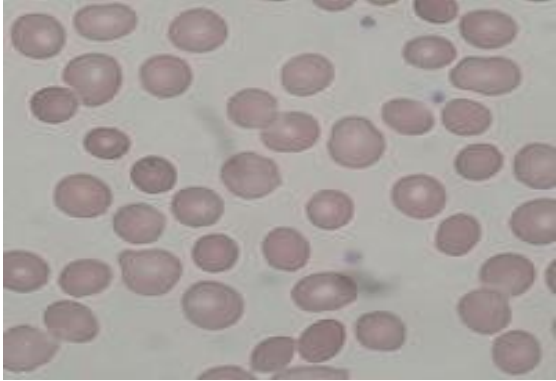
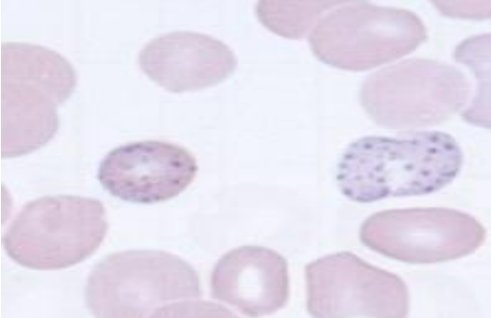
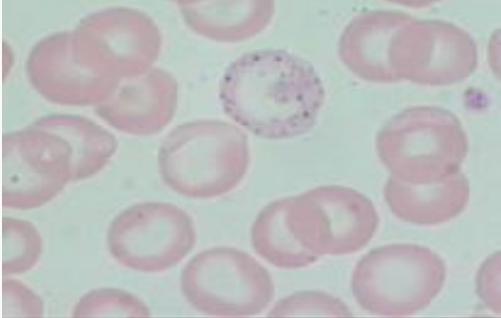
Acute graft versus host disease (GVHD)

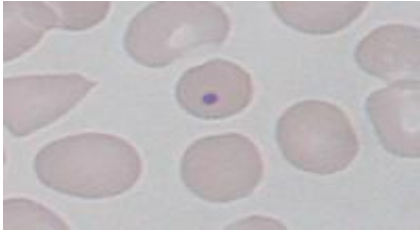
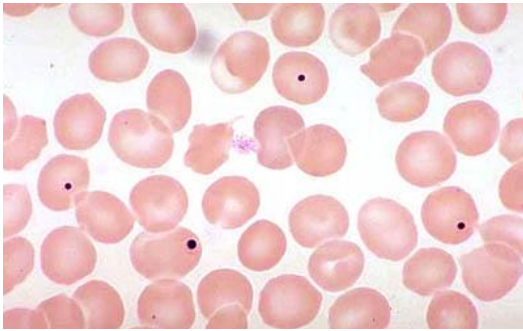
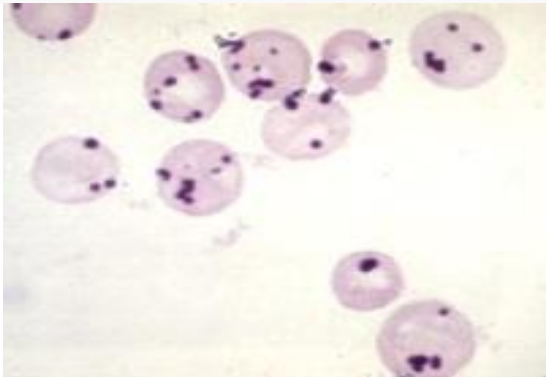
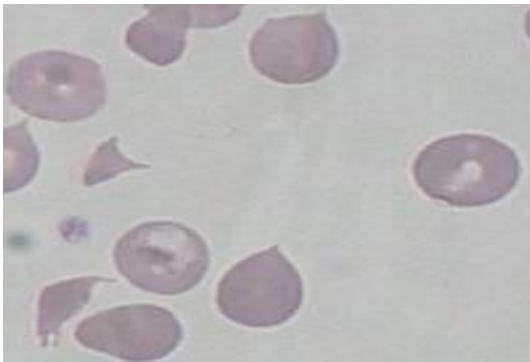
- ☒ occurs in the first 100 days post transplant
- ☒ GVHD is graded according to the Seattle system, and each organ involved is scored (skin, liver and gut).
- ☒ The standard initial treatment in the acute setting is high dose methylprednisolone. Action is needed quickly.
- ☒ If there is no response then more intensive immunosuppression is needed such as Campath or antilymphocyte globulin.

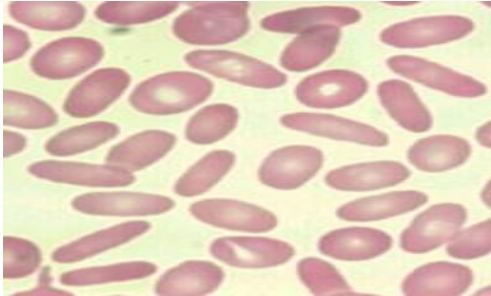
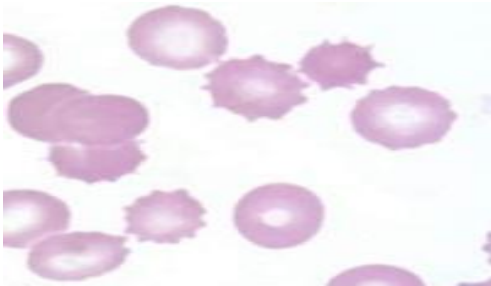
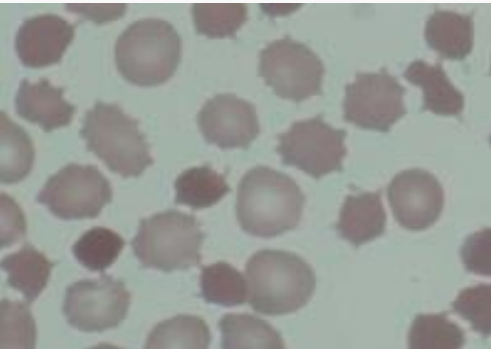
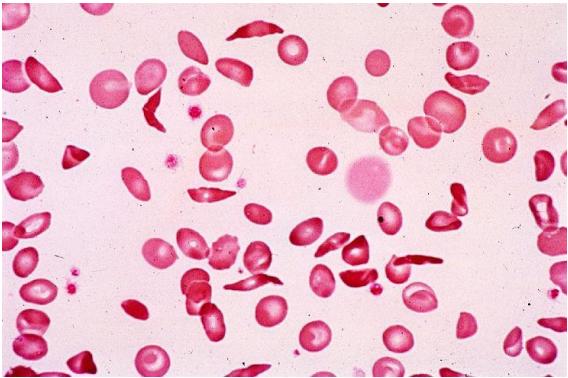
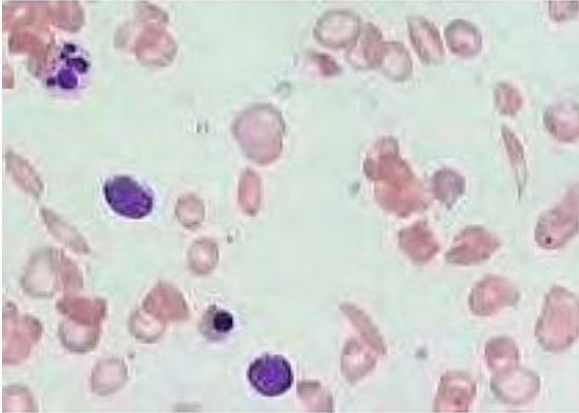
Chronic GVHD

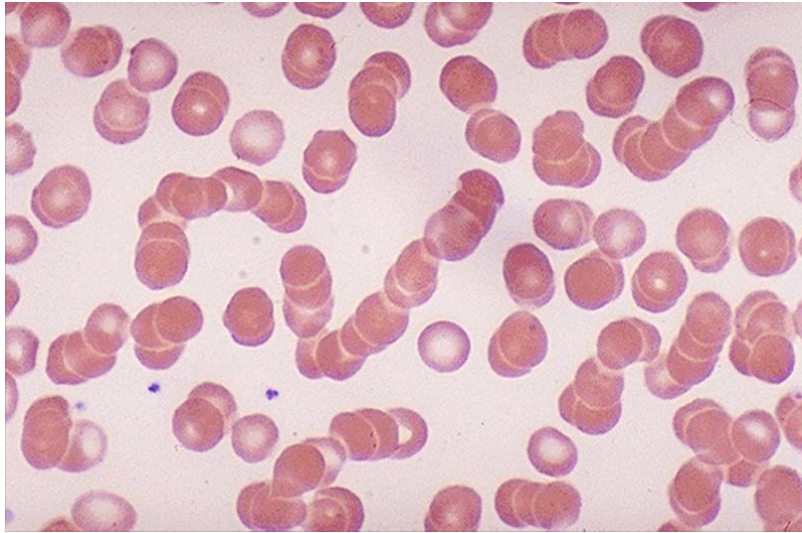
- ☒ Occurring 100-300 days post transplant.
- ☒ Oral prednisolone is the choice for chronic GVHD.

Blood films

Abnormality	Associated condition(s)	Appearance
Target cells	• Iron-deficiency anemia • Sickle-cell/thalassaemia • Hyposplenism • Liver disease	
'Tear-drop' poikilocytes	Myelofibrosis	
Spherocytes	• Hereditary spherocytosis • Autoimmune hemolytic anemia	
Basophilic stippling	• Lead poisoning • Thalassaemia	 

Abnormality	Associated condition(s)	Appearance
Howell-Jolly bodies	Hyposplenism (intracellular inclusion bodies consisting of remnants of DNA)	 
Heinz bodies	• G6PD deficiency • Alpha-thalassaemia	
Schistocytes ('helmet cells')	• Intravascular haemolysis • Mechanical heart valve • DIC	 

Abnormality	Associated condition(s)	Appearance
'Pencil' poikilocytes	Iron deficiency anemia	
Burr cells (echinocytes)	• Uraemia • Pyruvate kinase deficiency	
Acanthocytes	Abetalipoproteinemia Hyposplenism	
Sickle cell anaemia	This patient has sickle cell anaemia as evidenced by sickle cells (not seen in sickle cell trait [HbSC] or haemoglobin C [HbC] disease). Howell-Jolly bodies are also present, indicating hyposplenism.	 



The blood film shows red cell agglutination, suggesting the presence of cold agglutinin which is associated with

- Lymphoma (autoantibodies with anti-I specificity)
- *Mycoplasma pneumonia* (autoantibodies with anti-I specificity)

and, rarely

- Infectious mononucleosis (autoantibodies with anti-I specificity).

Other laboratory findings in cold agglutinin disease are similar to those in warm autoimmune haemolytic anaemia (red blood cell [RBC] polychromasia, unconjugated bilirubin, haptoglobin, and haemoglobinuria).

C3 is detected on the RBC surface by the direct antiglobulin test (DAT).

Cold agglutinin disease with RBC agglutination may be associated with Raynaud's phenomenon.

Hyposplenism

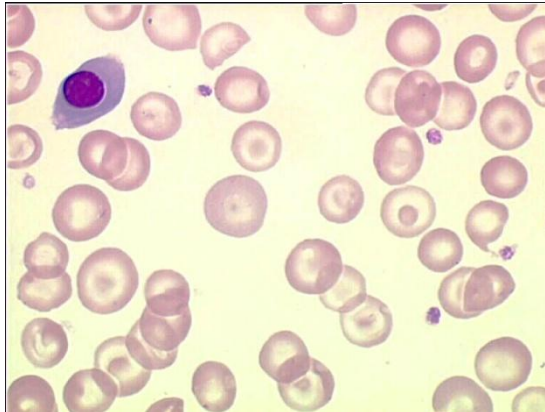
Causes:

- 1) splenectomy
- 2) sickle-cell
- 3) coeliac disease, dermatitis herpetiformis
- 4) Graves' disease
- 5) SLE
- 6) amyloid

Features:

- 1) **Howell-Jolly bodies** (intracellular inclusion bodies consisting of remnants of DNA)
- 2) Pappenheimer bodies
- 3) Siderocytes, siderotic granules
- 4) target cells
- 5) acanthocytes

The film shows target cells which are typically found in hyposplenism.



Iron-deficiency anemia:

- 1) target cells
- 2) 'pencil' poikilocytes
- 3) if combined with B12/folate deficiency a 'dimorphic' film occurs with mixed microcytic and macrocytic cells

Myelofibrosis: 'tear-drop' poikilocytes

Intravascular haemolysis: schistocytes

Megaloblastic anemia: hypersegmented neutrophils

The white cell

Eosinophilia

Causes of eosinophilia may be divided into pulmonary, infective and other

Pulmonary causes:

- 1) asthma
- 2) allergic bronchopulmonary aspergillosis
- 3) Churg-Strauss syndrome
- 4) Löffler's syndrome
- 5) tropical pulmonary eosinophilia
- 6) eosinophilic pneumonia
- 7) hypereosinophilic syndrome

Infective causes:

- 1) schistosomiasis
- 2) nematodes: Toxocara, Ascaris, Strongyloides
- 3) cestodes: Echinococcus

Other causes

- 1) drugs: sulfasalazine, nitrofurantoin
- 2) psoriasis/eczema
- 3) eosinophilic leukaemia (very rare)

Neutropenic sepsis

- Relatively a common complication of cancer therapy, usually chemotherapy.
- It may be defined as a neutrophil count of $< 0.5 \times 10^9$ in a patient who is having anticancer treatment and has one of the following:
 - ✓ a temperature higher than 38°C or
 - ✓ other signs or symptoms consistent with clinically significant sepsis

Prophylaxis:

- if it is anticipated that patients are likely to have a neutrophil count of $< 0.5 \times 10^9$ as a consequence of their treatment they should be offered a **fluoroquinolone**

Management: (as in on examination notes)

Assessment of the febrile patient with neutropenia should include:

- Assess for likely sites of infection from history and clinical examination and chest x ray.
- Comprehensive cultures of blood, urine, sputum, Hickman line (if present).
- If temperature more than 40°C for four to six hours or if the patient is hypotensive, blind broad-spectrum antibiotic therapy should be started (N.B. after taking cultures).
- Barrier nursing should be instituted if possible.
- Antibiotics should be continued for two to five days after the fever has settled and the neutrophil count has recovered.
- If fever persists after 48 hours despite antibiotic therapy, fungal (*Aspergillus*, *Candida*, *Pneumocystis*) or viral (*Cytomegalovirus* or CMV) infection should be considered.

- ✗ Although preferred antibiotic regimens for neutropenic fever vary from centre to centre, all operate on the same principles. The aim is to provide broad-spectrum coverage that includes cover for *Pseudomonas aeruginosa*.
- ✗ Dual therapy regimes are usually used. These utilise a broad-spectrum antibiotic (an antipseudomonal penicillin, carbapenem or ceftazidime) plus an anti-pseudomonal aminoglycoside. (although recent evidence suggests that monotherapy alone with a β lactam is sufficient)
- ✗ Typical regimens consist of anti-pseudomonal aminoglycoside (Gentamicin, or Amikacin), plus either:
 - Antipseudomonal penicillin: Piperacillin/tazobactam (Tazocin) or Ticarcillin/clavulanic acid (Timentin), or
 - Antipseudomonal carbapenem: Imipenem/cilastatin or Meropenem.
- ✗ If infection with *Staph. aureus* is suspected, the addition of vancomycin should be considered.
- ✗ there may be a role for G-CSF in selected patients

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- 1) **antibiotics** must be started **immediately**, do not wait for the WBC
- 2) NICE recommend starting empirical antibiotic therapy with **piperacillin/tazobactam (Tazocin) immediately**
- 3) many units add vancomycin if the patient has central venous access but NICE do not support this approach
- 4) following this initial treatment patients are usually assessed by a specialist and risk-stratified to see if they may be able to have outpatient treatment
- 5) if patients are still febrile and unwell after 48 hours an alternative antibiotic such as meropenem is often prescribed +/- vancomycin
- 6) if patients are not responding after 4-6 days the Christie guidelines suggest ordering investigations for fungal infections (e.g. HRCT), rather than just starting therapy antifungal therapy blindly
- 7) there may be a role for G-CSF in selected patients

See this link

[Neutropenic sepsis \(CG151\).](#)

Leucocyte alkaline phosphatase:

Rise in:

- pregnancy, oral contraceptive pill
- Cushing's syndrome, steroids
- Infections, leukaemoid reactions
- Myelofibrosis, polycythaemia rubra vera

Low in:

- chronic myeloid leukaemia
- pernicious anemia
- paroxysmal nocturnal haemoglobinuria
- infectious mononucleosis

Leukaemoid reaction:

- The leukaemoid reaction describes the presence of immature cells such as **myeloblasts**, **promyelocytes** and **nucleated RBCs** in the peripheral blood.
- This may be due to:
 1. infiltration of the bone marrow causing the immature cells to be 'pushed out' or
 2. sudden demand for new cells

Causes:

- 1) severe **infection**
- 2) severe **haemolysis**
- 3) massive **haemorrhage**
- 4) metastatic **cancer** with bone marrow infiltration

A relatively common clinical problem is differentiating **CML** from a leukaemoid reaction. The following differences may help:

Leukaemoid reaction	CML
• high leucocyte alkaline phosphatase score • toxic granulation (Dohle bodies) in the white cells • 'left shift' of neutrophils i.e. three or less segments of the nucleus	• low leucocyte alkaline phosphatase score

Myeloproliferative disorders
Polycythaemia
Myelofibrosis (myelosclerosis)
Myelodysplasia (MDS)

Polycythaemia

Polycythaemia may be relative, primary (polycythaemia rubra vera) or secondary

Relative causes:

- 1) dehydration
- 2) stress: Gaisbock syndrome

Primary:

- polycythaemia rubra vera

Secondary causes:

- 1) COPD
 - 2) altitude
 - 3) obstructive sleep apnoea
 - 4) CO chronic poisoning (e.g. heavy smoking)
 - 5) Rt to Lt shunt
 - 6) excessive erythropoietin:
 - ✓ cerebellar haemangioma,
 - ✓ hypernephroma,
 - ✓ hepatoma,
 - ✓ uterine fibroids: uterine fibroids may cause menorrhagia which in turn leads to blood loss - polycythaemia is rarely a clinical problem
- To differentiate between true (primary or secondary) polycythaemia and relative polycythaemia red cell mass studies are sometimes used.
 - In true polycythaemia the total red cell mass in males > 35 ml/kg and in women > 32 ml/kg

Polycythaemia Rubra Vera (PRV)

- A myeloproliferative disorder caused by clonal proliferation of a marrow stem cell leading to an **increase in red cell volume**.
- Often accompanied by **overproduction of neutrophils** and **platelets**.
- It has recently been established that **a mutation in JAK2 is present in approximately 95%** of patients with PRV and this has resulted in significant changes to the diagnostic criteria.
- The incidence of PRV peaks in the **sixth decade (50s)**.

Features:

- 1) plethoric appearance
- 2) hyperviscosity symptoms: headache, tinnitus, dizziness, blurring of vision & pruritis
- 3) HTN in a third of patients
- 4) **pruritus**, typically after a hot bath
- 5) **splenomegaly**
- 6) **haemorrhage** (secondary to abnormal platelet function)
- 7) **low ESR** and a **raised ALP** (leukocyte alkaline phosphatase)

Following history and examination, the British Committee for Standards in Haematology (BCSH) recommends the following tests are performed:

- 1) **full blood count/film** (raised haematocrit; neutrophils, basophils, platelets raised in half of patients)
- 2) **JAK2 mutation**
- 3) serum **ferritin**
- 4) **renal and liver function tests**

If the JAK2 mutation is negative and there is no obvious secondary causes the BCSH suggest the following tests:

- 1) red cell mass
- 2) arterial O2 saturation
- 3) serum erythropoietin level
- 4) abdominal ultrasound
- 5) bone marrow aspirate and trephine
- 6) erythroid burst-forming unit (**BFU-E**) culture
- 7) cytogenetic analysis

The diagnostic criteria for PRV have recently been updated by the BCSH. This replaces the previous PRV Study Group criteria.

JAK2-positive PRV - diagnosis requires both criteria to be present

Criteria	Notes
A1	- High haematocrit (>0.52 in men, >0.48 in women) OR - raised red cell mass (>25% above predicted)
A2	Mutation in JAK2

JAK2-negative PRV - diagnosis requires A1 + A2 + A3 + either another A or two B criteria

Criteria	Notes
A1	- haematocrit >0.60 in men, >0.56 in women OR - Raised red cell mass (>25% above predicted)
A2	Absence of mutation in JAK2
A3	No cause of secondary erythrocytosis
A4	Palpable splenomegaly
A5	Presence of an acquired genetic abnormality in the haematopoietic cells(excluding BCR-ABL)
B1	Thrombocytosis (platelet count >450 * 10 ⁹ /l)
B2	Neutrophil leucocytosis (neutrophil count > 10 * 10 ⁹ /l in non-smokers; > 12.5*10 ⁹ /l in smokers)
B3	Radiological evidence of splenomegaly
B4	- Endogenous erythroid colonies or - low serum erythropoietin

Polycythaemia rubra Vera management:

- 1) **Venesection** - first line treatment
- 2) **Aspirin**
- 3) **Hydroxyurea** -slight increased risk of secondary leukaemia
- 4) **Phosphorus-32 therapy**
- 5) Hyperviscosity: **urgent venesection**

Prognosis:

- ☒ thrombotic events are a significant cause of morbidity and mortality
- ☒ 5-15% of patients progress to myelofibrosis
- ☒ 5-15% of patients progress to AML (risk increased with chemotherapy treatment)

Thrombocytosis

Thrombocytosis is an abnormally high platelet count, usually $> 400 \times 10^9/l$.

Causes of thrombocytosis

- A) **Reactive:** platelets are an acute phase reactant - platelet count can increase in response to stress such as a severe infection or surgery
- B) **Malignancy**
- C) **Hyposplenism**
- D) **Essential thrombocytosis**, or
- E) Part of another myeloproliferative disorder such as **CML** or **PRV**

Essential Thrombocytosis

- One of the myeloproliferative disorders which **overlaps** with chronic myeloid leukaemia, polycythaemia rubra vera and myelofibrosis.
- **Megakaryocyte proliferation** results in an overproduction of platelets.

Features:

- 1) **platelet count $> 600 \times 10^9/l$**
- 2) **JAK2** mutation is found in around **50% of patients**
- 3) both thrombosis (venous or arterial) and haemorrhage can be seen
- 4) a characteristic symptom is **a burning sensation in the hands**

Management

- 1) **Hydroxyurea** (hydroxycarbamide) is widely used to reduce the platelet count
- 2) **Low-dose aspirin** may be used to reduce the thrombotic risk
- 3) **Anagrelide**
 - A second line drug in ET
 - has been associated with increased bone marrow fibrosis
- 4) **Interferon- α**
 - ⇒ is also used in younger patients
 - ⇒ Interferon has a use in ET in the setting of pregnancy.

Diagnosis of a myeloproliferative disorder:

- ☒ A bone marrow biopsy with ancillary studies would be useful in the diagnosis.
- ☒ There are also certain morphological features in the megakaryocytes on the bone marrow trephine which would be useful along with assessment of marrow iron stores.
- ☒ Hence bone marrow biopsy with molecular studies would be the most useful diagnostic test.

Myeloproliferative disorders
Polycythaemia
Myelofibrosis (myelosclerosis)
Myelodysplasia (MDS)

Myelofibrosis

- A myeloproliferative disorder
- Thought to be caused by hyperplasia of abnormal megakaryocytes
- The resultant release of platelet derived growth factor (PDGF) is thought to stimulate fibroblasts
- Haematopoiesis develops in the liver and spleen

Features:

- 1) Elderly person with symptoms of anemia e.g. Fatigue (the most common presenting symptom)
- 2) Hypermetabolic symptoms: weight loss, night sweats etc
- 3) Massive splenomegaly, liver enlargement not like spleen

Laboratory findings:

- 1) Anemia
- 2) High WBC and platelet count early in the disease
- 3) 'Tear-drop' poikilocytes on blood film
- 4) Unobtainable bone marrow biopsy - 'dry tap' therefore trephine biopsy needed
- 5) High urate and LDH (reflect increased cell turnover)

NB in hairy cell leukemia.....'dry tap' despite bone marrow hypercellularity

The candidate should recognise the abnormalities given in the question:

- anaemia
 - high WBC
 - thrombocytosis
 - a leucoerythroblastic blood film with characteristic tear drop cells, and
 - The presence of 'B'symptoms (weight loss and night sweats with splenomegaly).
-
- The differential diagnosis in this case is between the myeloproliferative disorders Chronic Myeloid Leukaemia (CML), Myelofibrosis and Essential Thrombocythaemia (ET).
 - CML and myelofibrosis can be very difficult to distinguish in the early stages on morphology alone or on clinical findings and the most useful test is **cytogenetic analysis** - most cases of **CML** are usually associated with **BCR-ABL translocation**, whereas this is not seen in myelofibrosis or ET (although other cytogenetic abnormalities are seen).
 - It is most useful to do cytogenetic analysis on a bone marrow sample rather than peripheral blood because the cellularity tends to be greater in the BM, giving lower failure rates of the test.
 - A bone marrow is indicated anyway because if this patient was BCR-ABL negative on the peripheral blood a bone marrow would be necessary to further facilitate diagnosis.

CML and myelofibrosis can be very difficult to distinguish in the early stages on morphology alone or on clinical findings and the most useful and **least invasive** for the patient is molecular analysis (PCR) of the peripheral blood - most cases of CML are usually associated with BCR-ABL translocation (t[9:22]), and this can be detected by PCR, whereas this is not seen in myelofibrosis or ET.

If present it can usually be detected in the peripheral blood, however in practice one would still eventually proceed to a bone marrow (BM) examination to assess morphology and you would still also perform conventional cytogenetics on the bone marrow (this is done on a bone marrow sample rather than peripheral blood because the cellularity tends to be greater in the BM, giving lower failure rates of the test).

Hematological Malignancies

Genetics:

Below is a brief summary of the common translocations associated with hematological malignancies

t(9;22) - Philadelphia chromosome (BCR-ABL):

- present in > 95% of patients with CML
- this results in part of the Abelson proto-oncogene being moved to the BCR gene on chromosome 22
- the resulting BCR-ABL gene codes for a fusion protein which has tyrosine kinase activity in excess of normal
- poor prognostic indicator in ALL

t(15;17):

- seen in acute promyelocytic leukaemia (M3)
- fusion of PML and RAR-alpha genes

t(8;14):

- seen in Burkitt's lymphoma
- MYC oncogene is translocated to an immunoglobulin gene

t(11;14)

- Mantle cell lymphoma
- deregulation of the cyclin D1 (BCL-1) gene

Haematological malignancies

Infections:

Viruses:

- EBV:
 - ⇒ Hodgkin's and Burkitt's lymphoma,
 - ⇒ nasopharyngeal carcinoma
- HIV-1:
 - ⇒ High-grade B-cell lymphoma
- HTLV-1:
 - ⇒ Adult T-cell leukaemia/lymphoma

Bacteria:

- *Helicobacter pylori*: gastric lymphoma (MALT)

Protozoa:

- malaria: Burkitt's lymphoma

Acute myeloid leukaemia

- Acute myeloid leukaemia is the more common form of acute leukaemia in adults.
- may occur as **primary** disease or as **secondary** transformation of a myeloproliferative disorder:
 - ☒ 5-15% of PRV progress to AML (risk increased with chemotherapy treatment)
 - ☒ Essential thrombocytosis is one of the myeloproliferative disorders which **overlaps** with chronic myeloid leukaemia, polycythaemia rubra vera and myelofibrosis.
 - ☒ CML May undergo blast transformation (AML in 80%, ALL in 20%)

Poor prognostic features:

- 1) > 60 years
- 2) > 20% blasts after first course of chemotherapy.
- 3) cytogenetics: deletions of chromosome **5** or **7**

Classification - French-American-British (FAB)

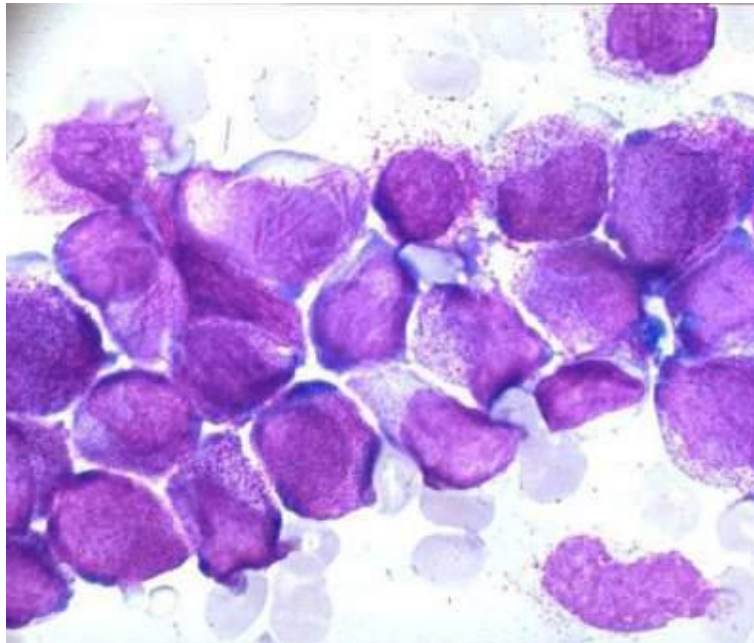
- The FAB classification system of acute myeloid leukaemias is based on the type of cell from which the leukaemia develops and the stage of cellular differentiation/maturation.
- Eight categories of AML are recognised:
 - **M0** (**undifferentiated AML**)
 - M1 (myeloblastic - immature)
 - M2 (myeloblastic - **mature**)
 - **M3** (**promyelocytic**; acute promyelocytic leukaemia; APL)
 - M4 (myelomonocytic)
 - **M5** monocytic (**gingival hyperplasia**)
 - M6 (erythroid)
 - **M7** (**megakaryoblastic**).
- **Subtype M2 (acute myeloblastic leukaemia)**
 - ⇒ the most common (25% of adult AML)
 - ⇒ associated with a t(8;21) translocation
- **Subtypes M0, M6, and M7**
 - ⇒ carry the **worst prognosis**
- **AML M3 (acute promyelocytic leukaemia; APL)**
 - ⇒ usually associated with a t(**15;17**) translocation
 - ⇒ Promyelocytes cytoplasm is heavily granulated.
 - ⇒ These granules contain pro-coagulant factors that render patients with APL susceptible to the development of DIC.
 - ⇒ Despite this, APL has the best prognosis of all the subtypes of AML.
 - ⇒ Unlike the other AML subtypes, APL is treated with **all-trans retinoic acid** (ATRA)
- **Acute myelomonocytic leukaemia (AML M4)**
 - ⇒ associated with a t(**16;16**) translocation

Acute promyelocytic leukaemia

- Acute promyelocytic leukaemia (APML) is the M3 subtype of AML.
- Importance of identifying APML lies in both the presentation (classically DIC) and management
- APML is associated with the t(15;17) translocation which causes **fusion** of the PML and RAR-alpha genes.

Features:

- 1) Presents younger than other types of AML (average = 25 years old)
- 2) **DIC** or **thrombocytopenia** often at presentation
- 3) **Good prognosis**
- 4) **Auer rods** (seen with myeloperoxidase stain)



The slide shows promyelocytes:

- the cells have large, dark-staining nuclei and granular cytoplasm;
- the rod-shaped projections in the cells are **Auer rods**
- Auer rods are elongated, bluish-red rods composed of fused lysosomal granules, seen in the cytoplasm of myeloblasts, promyelocytes and monoblasts.
- They may be single or multiple.
- The presence of large numbers of promyelocytes with Auer rods and cytoplasmic granules in the peripheral circulation is typical of promyelocytic leukaemia.

Gingival hyperplasia

Drug causes of gingival hyperplasia

- 1) phenytoin
- 2) ciclosporin
- 3) calcium channel blockers (especially nifedipine)

Other causes of gingival hyperplasia include

- acute myeloid leukaemia (**myelomonocytic** and **monocytic** types)

Chronic myeloid leukaemia

- The **Philadelphia chromosome** is present in more than **95% of patients** with CML.
- It is due to a translocation between the long arm of **chromosome 9 and 22** - **t(9:22)(q34; q11)**
- This results in part of the ABL proto-oncogene from chromosome 9 being fused with the BCR gene from chromosome 22.
- The resulting BCR-ABL gene codes for a fusion protein which has **tyrosine kinase activity** in excess of normal

Presentation (40-50 years):

- 1) middle-age
- 2) anemia, weight loss, abdominal discomfort
- 3) splenomegaly may be marked
- 4) spectrum of **myeloid cells** seen in peripheral blood (**mature & immature**)
- 5) **decreased** leukocyte **ALP**
- 6) May undergo blast transformation (AML in 80%, ALL in 20%)

Management:

1) **Imatinib: First-line treatment**

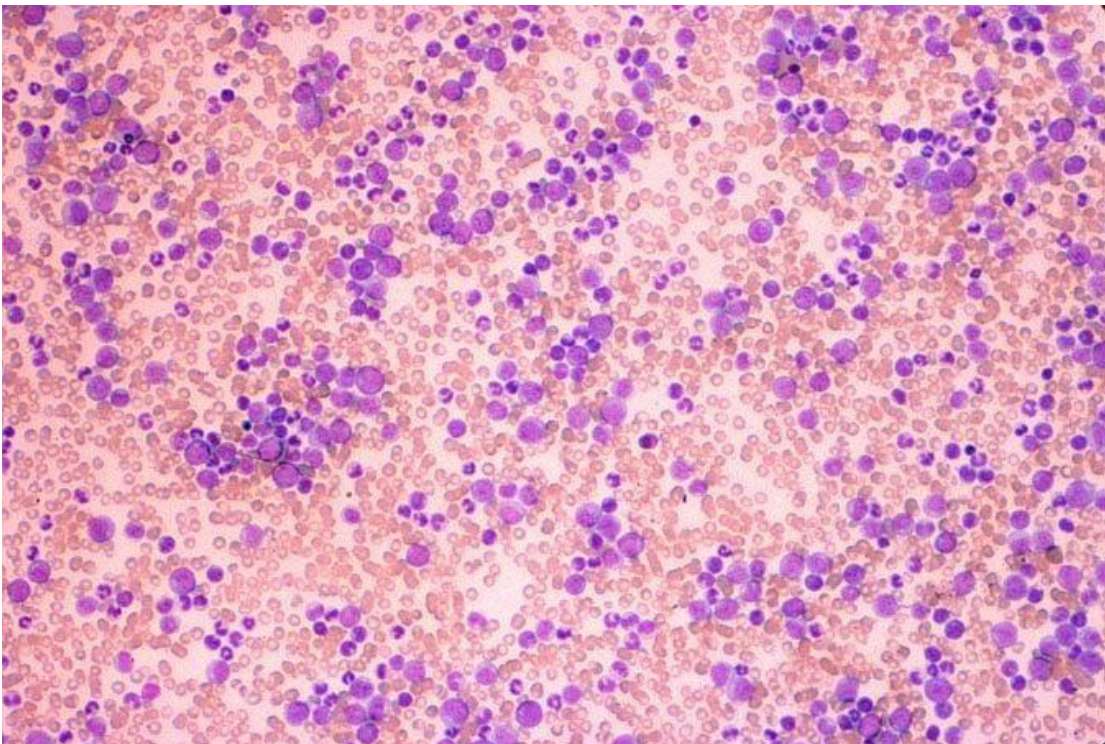
- ⇒ **inhibitor of the tyrosine kinase** associated with the BCR-ABL defect
- ⇒ very high response rate in chronic phase CML

2) **Hydroxyurea** (also used in PRV & essential thrombocytosis)

3) **Interferon-alpha**

4) **Allogenic bone marrow transplant:** If remission is not achieved with Imatinib, then;

- ☒ In a patient under 60-65 years, an allogeneic transplant would be considered if there was a matched sibling donor;
- ☒ In a 50-year-old patient or younger a matched unrelated donor transplant



The blood film shows both mature (neutrophils) and immature forms in various stages of differentiation (myelocytes and metamyelocytes) and hence favours chronic myeloid leukaemia (CML). In acute myelogenous leukemia (AML) one would expect only immature blasts.

Acute lymphoblastic leukaemia (ALL)

Prognostic features

Good prognostic factors:

- 1) French-American-British (FAB) L1 type
- 2) common ALL
- 3) pre-B phenotype
- 4) low initial WBC
- 5) del(9p)

Poor prognostic factors:

- 1) FAB L3 type
- 2) T or B cell surface markers
- 3) Philadelphia translocation, t(9;22)
- 4) age < 2 years or > 10 years
- 5) non-Caucasian
- 6) male sex
- 7) CNS involvement
- 8) high initial WBC (e.g. > $100 \times 10^9/l$)

Chronic lymphocytic leukaemia (CLL)

Caused by a **monoclonal proliferation** of **well-differentiated lymphocytes** which are almost always **B-cells** (99%)

Features:

- 1) Often none (common discovery on routine blood tests).
- 2) constitutional: anorexia, weight loss
- 3) bleeding, infections
- 4) Lymphadenopathy (cervical) more marked than CML

Complications:

- 1) hypogammaglobulinaemia leading to **recurrent infections** (**Regular infusions of IG**)
- 2) **warm autoimmune haemolytic anemia** in 10-15% of patients
- 3) **transformation** to high-grade lymphoma (**Richter's transformation**) (low grade lymphoma)

Investigations:

- 1) Blood film: **smudge cells**
- 2) **Immunophenotyping**

Flow cytometry showing a specific pattern of monoclonal B cell proliferation (CD19/5 co expressing, CD23 positive, light chain restricted B cell population) is diagnostic of CLL.

Poor prognostic factors: (median survival 3-5 years)

- 1) male sex
- 2) age > 70 years
- 3) lymphocyte count > 50
- 4) prolymphocytes comprising > 10% of blood lymphocytes
- 5) lymphocyte doubling time < 12 months
- 6) raised LDH
- 7) **CD38** expression positive

Chromosomal changes:

A) Deletion of the long arm of chromosome 13 (del 13q) :

- It is the **most common abnormality**, being seen in around **50% of patients**.
- It is associated with a **good prognosis**

B) Deletions of part of the short arm of chromosome 17 (del 17p)

- These are seen in around **5-10% of patients**
- associated with a **poor prognosis**

Indications for treatment in CLL:

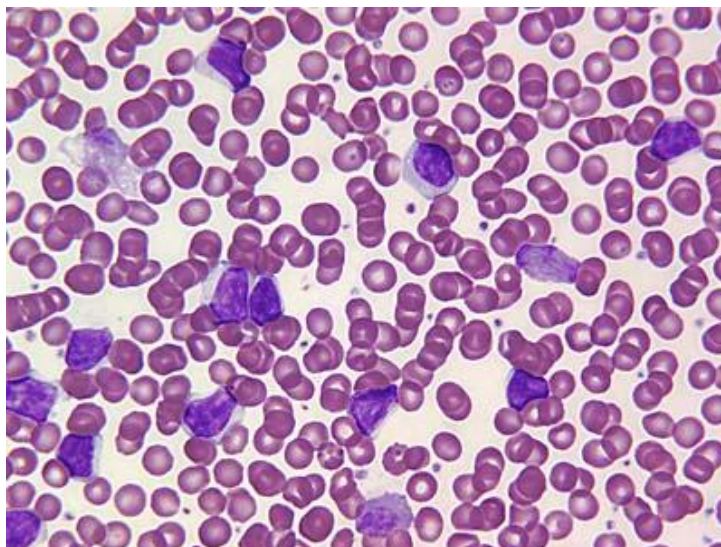
- 1) **Progressive marrow failure:** development or worsening of **anemia** and/or **thrombocytopenia**
- 2) Autoimmune cytopaenias e.g. **ITP**, **AIHA**
- 3) Massive (>10 cm) or progressive **lymphadenopathy**
- 4) Massive (>6 cm) or progressive **splenomegaly**
- 5) **Progressive lymphocytosis:**
 - ☒ > 50% increase over **2 months** or
 - ☒ lymphocyte doubling time < **6 months**
- 6) **Systemic symptoms:**
 - ⇒ weight loss > 10% in previous 6 months,
 - ⇒ fever >38 C for > 2 weeks,
 - ⇒ extreme fatigue, night sweats

Management:

- 1) patients who have no indications for treatment are **monitored only** with regular blood counts
- 2) First line treatment is with chlorambucil. Prednisolone can be added to this but is of no proven benefit, although it sometimes makes the patients feel better.
- 3) Fludarabine is second line treatment.
- 4) **Fludarabine**, **cyclophosphamide** and **rituximab** (**FCR**)
- 5) Alemtuzumab (Anti-Cd52)

Fludarabine

- a purine analogue that is phosphorylated intracellularly
- All of the purine analogues cause myelosuppression
- There is a significantly higher risk of patients developing *Pneumocystis jirovecii* pneumonia while on treatment.
- Use of prophylactic co-trimoxazole (Septrin) has dramatically reduced the frequency of this severe opportunistic infection in these patients.
- Co-trimoxazole should be continued after chemotherapy until the CD4 counts exceeds 200 cells/mm³ ($0.2 \times 10^9/L$)



CLL progressive accumulation of functionally incompetent lymphocytes
Morphologically in the peripheral blood, these cells resemble mature lymphocytes.

Hairy cell leukaemia

- A rare malignant proliferation disorder of B cells.
- It is more common in males (4:1)

Features:

- 1) Pancytopenia
- 2) Splenomegaly
- 3) Skin vasculitis in 1/3 patients
- 4) 'Dry tap' despite bone marrow hypercellularity
- 5) Tartrate resistant acid phosphatase (TRAP) stain positive

Management:

- 1) Chemotherapy is first-line: cladribine, pentostatin
- 2) Immunotherapy is second-line: rituximab, interferon-alpha

Interferons (IFN)

- Cytokines released by the body in response to viral infections and neoplasia.
- They are classified according to cellular origin and the type of receptor they bind to:
 - 1) IFN-alpha and IFN-beta bind to type 1 receptors whilst
 - 2) IFN-gamma binds only to type 2 receptors.
- IFN-alpha is produced by leucocytes and has an antiviral action.
- It has been shown to be useful in management of:
 - 1) Hepatitis B & C,
 - 2) Kaposi's sarcoma,
 - 3) Metastatic renal cell cancer,
 - 4) Hairy cell leukaemia,
 - 5) CML & essential thrombocytosis

Hodgkin's lymphoma

- Malignant proliferation of **lymphocytes** Characterised by presence of the **Reed-Sternberg cell**.
- It has a **bimodal age** distributions being most common in the **third** and **seventh decades**

Features:

- 1) lymphadenopathy (75%) - painless, non-tender, asymmetrical
- 2) systemic (25%): pruritus, weight loss, , night sweats, fever (Pel-Ebstein)
- 3) alcohol pain in HL
- 4) normocytic anemia, eosinophilia
- 5) LDH raised

Histological classification:

Type	Frequency	Prognosis	Notes
Nodular sclerosing	Most common (around 70%)	Good prognosis	• More common in women. • Associated with lacunar cells
Mixed cellularity	Around 20%	Good prognosis	Associated with a large number of Reed-Sternberg cells
Lymphocyte predominant	Around 5%	Best prognosis	
Lymphocyte depleted	Rare	Worst prognosis	

'B' symptoms also imply a poor prognosis

- 1) weight loss > 10% in last 6 months
- 2) fever > 38 C
- 3) night sweats

Other factors associated with a poor prognosis identified in a 1998 NEJM paper included:

- 1) Age > 45 years
- 2) Male
- 3) Stage iv disease
- 4) Hemoglobin < 10.5 g/dl
- 5) White blood count > 15,000
- 6) Lymphocyte count < 600 or < 8%
- 7) Albumin < 40 g/l

*Reed-Sternberg cells with nuclei surrounded by a clear space

Hodgkin's lymphoma: staging:

Ann-Arbor staging of Hodgkin's lymphoma

- ☒ **I:** single lymph node
- ☒ **II:** 2 or more lymph nodes/regions on same side of diaphragm
- ☒ **III:** nodes on both sides of diaphragm
- ☒ **IV:** spread beyond lymph nodes

Each stage may be subdivided into A or B

- ☒ **A** = no systemic symptoms **other than pruritus**
- ☒ **B** = weight loss > 10% in last 6 months, fever > 38°C, night sweats (poor prognosis)

Management:

- ABVD chemotherapy
- Relapsed Hodgkin lymphoma in an early relapse (less than one year) must be managed aggressively with **salvage chemotherapy** followed by **BEAM conditioned autologous stem cell transplantation** as **the established gold standard**.

Burkitt's lymphoma

- Burkitt's lymphoma is a high-grade B-cell lymphoplastic lymphoma neoplasm.
- Burkitt's lymphoma is associated with the **c-myc gene translocation**, usually **t(8:14)**
- There are two major forms:

1) **Endemic (African) form:**

- ☒ typically involves **maxilla** or **mandible**
- ☒ **The Epstein-Barr virus** (EBV) is strongly implicated in the development of the African form of Burkitt's lymphoma and to a lesser extent the sporadic form.

2) **Sporadic form:**

- ☒ Abdominal tumours (e.g. **ileo-caecal**) are the most common form.
- ☒ More common in patients with **HIV**

Management:

1) **Intensive chemotherapy.**

⇒ This tends to produce a rapid response which may cause 'tumour lysis syndrome'.

2) **Rasburicase :**

- A recombinant version of **urate oxidase**,
- An enzyme which catalyses the conversion of **uric acid** to **allantoin** is often given before the chemotherapy to reduce the risk of 'tumour lysis syndrome'.
- allantoin is 5-10 times more soluble than uric acid, so renal excretion is more effective

Complications of tumour lysis syndrome:

- 1) Hyperuricaemia
- 2) Hyperkalaemia
- 3) Hyperphosphataemia
- 4) Hypocalcaemia
- 5) Acute renal failure

Asymptomatic patients with low grade lymphoma such as follicular lymphoma (grade 1 and 2) can be observed closely.

The value of intensive chemotherapy is questionable in asymptomatic patients. No long term survival benefit has been demonstrated with this approach.

Paraproteinaemia

Causes of paraproteinaemia:

- 1) Myeloma
- 2) Waldenstrom's macroglobulinaemia
- 3) Monoclonal gammopathy of uncertain significance (MGUS)
- 4) Benign monoclonal gammopathy
- 5) Amyloidosis
- 6) CLL, lymphoma
- 7) Heavy chain disease
- 8) POEMS

Benign monoclonal gammopathy:

- 1) Non-lymphoid malignancy (e.g. colon, breast)
- 2) Infections (CMV, hepatitis)
- 3) Autoimmune disorders (RA, SLE)

Myeloma

- Neoplastic proliferation of **bone marrow plasma cells**
- peak age = 60-70 years, **equal sex ratio**

Monoclonal products produced

- **IgG** (50-60%)
- **IgA** (20-30%)
- **Light chain disease** (20%)

Clinical features:

- 1) Bone disease:
 - ✓ Bone pain,
 - ✓ Osteoporosis + pathological fractures (typically vertebral),
 - ✓ Osteolytic lesions
- 2) Lethargy
- 3) Infection
- 4) **Hypercalcaemia**
- 5) **Renal failure**
- 6) **Amyloidosis** e.g. Macroglossia,
- 7) **Carpal tunnel syndrome**;
- 8) Neuropathy;
- 9) **Hyperviscosity**

Diagnosis of Myeloma in symptomatic myeloma:

All 3 of the following are needed for a diagnosis of

- 1) **Monoclonal plasma cells in marrow**: at least 10%
- 2) **Monoclonal protein** in **serum** or **urine** (but if non-secretory at least 30% monoclonal plasma cells in the bone marrow)
- 3) Myeloma-related organ or tissue impairment (hypercalcaemia, anemia and lytic bone lesions)

Diagnosis of asymptomatic myeloma: requires both of the following:

- 1) Monoclonal plasma cells in the marrow: at least 10%, OR monoclonal protein at least 30 g/L
- 2) Absence of myeloma related organ/tissue dysfunction

Treatment:

A) Asymptomatic myeloma: The mainstay treatment is **observation** until they become symptomatic

B) Symptomatic myeloma:

☒ >65 years:

⇒ **Thalidomide** (teratogenic) in combination with **corticosteroid** and an **alkylating agent**.

⇒ Bortezomib is used in patients intolerant to thalidomide or if contra-indicated.

☒ < 65: **stem cell transplantation** may be trialed.

☒ if hyperviscosity syndrome e.g. visual disturbance----> **Plasmapheresis**

Myeloma prognosis:

- 1) **B2-microglobulin** is a useful marker of prognosis - **raised** levels imply **poor prognosis**.
- 2) **Low albumin** are also associated with a **poor prognosis**

International prognostic index

Stage	Criteria	Median survival (months)
I	B2 microglobulin < 3.5 mg/l Albumin > 35 g/l	62 (> 5 years)
II	Not I or III	45 (about 4 years)
III	B2 microglobulin > 5.5 mg/l	29 (about 2.5 years)

Hypercalcaemia in myeloma

- 1) **Primary factor:** due primarily to **increased osteoclastic bone resorption** caused by local cytokines (e.g. IL-1, TNF) released by the myeloma cells
- 2) **Much less common contributing factors:**
 1. Impaired renal function,
 2. Increased renal tubular calcium reabsorption and
 3. Elevated PTH-rP levels

Patients with myeloma with high paraprotein levels and symptoms related to hyperviscosity should have urgent plasma exchange, chemotherapy needs to then be instituted promptly to control the disease process and prevent symptoms reoccurring. If transfusion is absolutely necessary then an exchange transfusion should be done.

Waldenstrom's macroglobulinaemia

- An uncommon condition seen in **older men**.
- It is a lymphoplasmacytoid malignancy characterised by the secretion of a **monoclonal IgM** paraprotein

Features:

- 1) Monoclonal IgM paraproteinaemia (IgM is large & intravascular) so causes **hyperviscosity** syndrome e.g. **visual disturbance** (**TTT Plasmapheresis**)
- 2) Systemic upset: weight loss, lethargy
- 3) Hepatosplenomegaly, lymphadenopathy
- 4) Cryoglobulinaemia e.g. **Raynaud's**

Although IgM, the largest immunoglobulin and nearly 100% intravascular, is most likely to cause hyperviscosity, IgA and IgG3 tend to aggregate and are more likely than other isotypes or subclasses to be associated with hyperviscosity.

MGUS

- Monoclonal gammopathy of undetermined significance (MGUS)
- Also known as **benign paraproteinaemia** and **monoclonal gammopathy**.
- It is a common condition that causes a paraproteinaemia and is often mistaken for myeloma.
- Differentiating features are listed below.
- Around 10% of patients eventually develop myeloma at 5 years
- 50% develop myeloma at 15 years

Features:

- 1) usually asymptomatic
- 2) no bone pain or increased risk of infections
- 3) around 10-30% of patients have **demyelinating neuropathy**

Differentiating features from myeloma

- 1) normal immune function
- 2) normal B2 microglobulin levels
- 3) lower level of paraproteinaemia than myeloma (e.g. < 30g/l IgG, or < 20g/l IgA)
- 4) stable level of paraproteinaemia
- 5) no clinical features of myeloma (e.g. lytic lesions on x-rays or renal disease)

Amyloidosis

- **Extracellular** deposition of an **insoluble fibrillar protein** termed amyloid
- The accumulation of amyloid fibrils leads to tissue/organ dysfunction
- Amyloid is derived from many different precursor proteins:
 - A) **Fibrillar component**
 - B) **Non-fibrillary protein:**
 - 1) amyloid-P component, derived from the acute phase protein **serum amyloid P**
 - 2) apolipoprotein E and
 - 3) heparan sulphate proteoglycans

Classification:

- systemic or localized
- further characterised by precursor protein (e.g. AL in myeloma - A for Amyloid, L for immunoglobulin Light chain fragments)

A) AL amyloid:

- L for immunoglobulin Light chain fragment
- due to **myeloma**, **Waldenstrom's**, **MGUS**
- features include:
 - ☒ cardiac and neurological involvement,
 - ☒ macroglossia,
 - ☒ periorbital ecchymoses

B) AA amyloid:

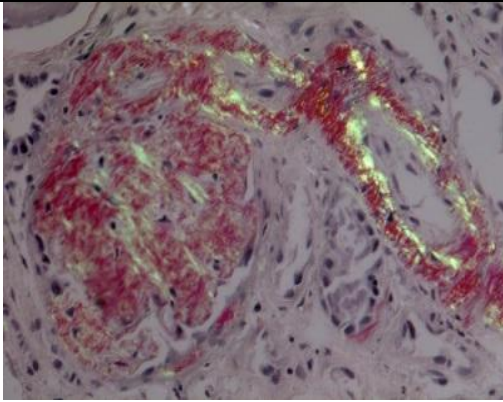
- A for precursor serum amyloid A protein,
- an acute phase reactant seen in **chronic infection/inflammation**
 - ☒ e.g. TB, bronchiectasis, rheumatoid arthritis
- features: **renal involvement** most common feature

C) Beta-2 microglobulin amyloidosis:

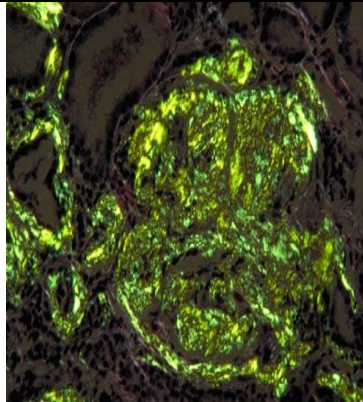
- precursor protein is beta-2 microglobulin, part of the MHC
- associated with patients on renal dialysis

Diagnosis:

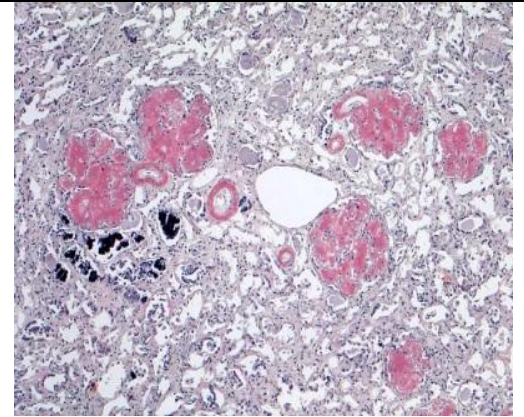
- Congo red staining: **apple-green** birefringence
- serum amyloid precursor (**SAP**) scan
- rectal biopsy



Renal amyloid with congo red staining - apple-green birefringence



Renal amyloid with congo red staining - apple-green birefringence



Congo red staining. Amyloid deposits are seen in both the arteries/arterioles and within the glomerulus. The deposit of amyloid within the mesangium is not dissimilar to the nodular lesions seen in diabetic nephropathy

Haemostasis and thrombosis
Haemostasis Vascular disorders
Platelet disorders
Inherited coagulation disorders
Acquired coagulation disorders
Thrombosis

Thrombocytopenia

Causes of severe thrombocytopenia

- 1) ITP
- 2) DIC
- 3) TTP
- 4) haematological malignancy

Causes of moderate thrombocytopenia:

- 1) heparin induced thrombocytopenia (HIT)
- 2) drug-induced (e.g. quinine, thiazides, diuretics, sulphonamides, aspirin,)
- 3) alcohol, liver disease
- 4) hypersplenism
- 5) viral infection (EBV, HIV, hepatitis)
- 6) pregnancy
- 7) SLE/antiphospholipid syndrome
- 8) vitamin B12 deficiency

Idiopathic thrombocytopenic purpura (ITP)

- ITP is an immune mediated reduction in the platelet count.
- Antibodies are directed against the glycoprotein IIb/IIIa or Ib-V-IX complex.
- ITP can be divided into acute and chronic forms:

A) Acute ITP:

- more commonly seen in children
- equal sex incidence
- may follow an infection or vaccination
- usually runs a self-limiting course over 1-2 weeks

B) Chronic ITP:

- more common in young/middle-aged women
- tends to run a relapsing-remitting course

Investigations:

- 1) antiplatelet autoantibodies (usually IgG)
- 2) Bone marrow aspiration shows megakaryocytes in the marrow. This should be carried out prior to the commencement of steroids in order to rule out leukaemia

Management:

- 1) oral prednisolone (80% of patients respond)
- 2) splenectomy if platelets < 30 after 3 months of steroid therapy
- 3) IVIGs
- 4) immunosuppressive drugs e.g. Cyclophosphamide
- 5) Although platelet transfusions are not efficacious in ITP, they are useful in life threatening bleeding, together with high doses IV steroids and IVIG.

Evan's syndrome: ITP in association with autoimmune haemolytic anemia (AIHA)

Thrombotic thrombocytopenic purpura(TTP)

- abnormally large and sticky multimers of vW factor cause platelets to clump within vessels
- in TTP there is a **deficiency of ADAMTS13** (a metalloprotease enzyme) which breakdowns large multimers of vWF

Features:

- 1) typically adult females
- 2) fever
- 3) fluctuating neuro signs (**microemboli**)
- 4) MAHA(microangiopathic haemolytic anemia), thrombocytopenia, renal failure

Causes:

- 1) post-infection e.g. urinary, gastrointestinal
- 2) pregnancy
- 3) drugs: ciclosporin, oral contraceptive pill, penicillin, acyclovir, clopidogrel,
- 4) tumours
- 5) SLE, HIV

Mortality is **90%** unless diagnosed and treated urgently, falling to **10%** if treated appropriately.

Management:

- 1) No antibiotics - may worsen outcome- **No Platelet transfusion** $\Rightarrow$ is **deleterious**.
- 2) **The treatment of choice plasma exchange with fresh frozen plasma**
- 3) FFP can be given until Plasmapheresis
- 4) Steroids, immunosuppressants (in chronic TTP decrease the chance of relapse.)
- 5) Vincristine

In TTP, the coagulation and D-dimers are usually normal: this can be used to differentiate TTP from DIC.

In DIC there is the microangiopathic haemolytic anemia with thrombocytopenia, but the coagulation is abnormal due to the consumptive process - classically hypofibrinogenaemia develops, **high D-Dimer & FDP**

Haemolytic uraemic syndrome (HUS)

Haemolytic uraemic syndrome is generally seen in young children and produces a triad of:

- 1) acute renal failure
- 2) microangiopathic haemolytic anemia
- 3) thrombocytopenia

Causes:

- post-dysentery - **classically E coli 0157:H7** ('verotoxigenic', 'enterohaemorrhagic')
- tumours
- pregnancy
- ciclosporin, the Pill
- SLE, HIV

Investigations:

- full blood count: anemia, thrombocytopaenia, fragmented blood film
- U&E: acute renal failure
- stool culture

Management:

- treatment is **supportive** e.g. Fluids, blood transfusion and dialysis if required
- there is **no role for antibiotics**, despite the preceding diarrhoeal illness in many patients
- The indications for plasma exchange in HUS are complicated. As a general rule **plasma exchange is reserved for severe cases of HUS not associated** with diarrhea
- ☒ HUS is a complication of infection with verocytotoxin producing *Escherichia coli* usually of the serotype 0157:H7.
- ☒ Toxins produced in the intestine enter the blood and bind to endothelial cells in target organs.
- ☒ Endothelial cell damage leads to platelet and fibrin deposition with resultant fragmentation of circulating red blood cells and microvascular occlusion.
- ☒ The syndrome has also been reported after infections with coxsackie, echovirus and *Shigella*.
- ☒ HUS is characterised by the sudden onset of haemolytic anaemia with fragmentation of red blood cells, thrombocytopenia and acute renal failure after a prodromal illness of acute gastroenteritis often with bloody diarrhoea.
- ☒ Clinical signs include increasing pallor, haematuria, oliguria and purpura. Jaundice is occasionally seen. Hypertension may be present.
- ☒ Typical results show anaemia, thrombocytopenia, and often a neutrophilia. Blood film shows fragmented erythrocytes.
- ☒ There is **normal coagulation and fibrinogen**.
- ☒ Neurological complications include:
 - Stroke, seizure and coma occur in 25% of patients
 - Rarely pancreatitis, and
 - Pleural and pericardial effusions.

- ✗ Approximately 5% of patients will develop end stage renal failure.
- ✗ Long term renal sequelae range from proteinuria to chronic renal failure.
- ✗ Therapy is supportive with:
 - Correction of anaemia
 - Correction of uraemia by early dialysis
 - Strict fluid balance
 - Treatment of hypertension.

Major differential diagnosis is:

- 1) Sepsis with DIC - presents with abnormalities of clotting parameters.
 - 2) TTP - thrombotic thrombocytopenic purpura presents with microangiopathic haemolytic anaemia, thrombocytopenic purpura, neurologic abnormalities, fever, and renal disease.
- ✗ Renal abnormalities tend to be more severe in HUS.
 - ✗ Although once considered variants of a single syndrome, recent evidence suggests that the pathogenesis of TTP and HUS is different.
 - ✗ Patients with TTP lack a plasma protease that is responsible for the breakdown of von Willebrand factor (vWF) multimers and these accumulate in the plasma. The activity of this protease is normal in patients with HUS.
 - ✗ Until the test for vWF protease activity becomes available, differentiation between HUS and TTP is based on the presence of central nervous system involvement in TTP and the more severe renal involvement in HUS.
 - ✗ In HUS 90% of patients are children and a history of prodromal diarrhoeal illness is more common.
 - ✗ The therapy of choice for TTP is **plasma exchange with fresh frozen plasma**.

Heparin-induced thrombocytopaenia (HIT)

- immune mediated - antibodies form which cause the activation of platelets
- Usually does not develop until after **5-10 days** of treatment but can occur earlier if previously exposed.
- despite being associated with low platelets HIT is actually a **prothrombotic condition**

Features:

The central features are **thrombocytopenia** and **increased thrombin production**, the latter being a risk factor for the development of both **arterial** and **venous thrombosis**.

- 1) **a greater than 50% reduction in platelets**,
- 2) **thrombosis** and
- 3) **skin allergy**

Treatment options include

- ☒ Alternative anticoagulants such as **lepirudin** and **danaparoid**

There are two types of HIT:

Type 1:

- a non-immune mediated reaction occurring soon after the initial administration of heparin (within two days) and is due to a direct effect of the drug on platelets
- Type 1 HIT is a self-limiting condition and the platelet count will normalize with continued heparin administration.

Type 2 HIT:

- an immune mediated condition
- gives rise to a limb and life threatening pro-thrombotic state
- It typically arises 5 to 10 days after starting heparin therapy
- Patients may develop both venous and arterial thromboses,
- low platelet counts and mild abnormalities of coagulation
- The **D-dimer** level is **raised** due to widespread thrombus formation.

- In general a platelet count of $10-20 \times 10^9 / L$ is safe for most procedures.
- The exceptions to this are major surgery and procedures involving the CNS and eyes. In the latter cases, the platelet count should be above $50 \times 10^9 / L$.

DIC

- In DIC there is the microangiopathic haemolytic anaemia with thrombocytopenia, and the coagulation is abnormal due to the consumptive process – classically hypofibrinogenaemia develops.
- There are a large number of causes of DIC. One such cause is tissue damage, causing release of tissue factor, such as might occur in trauma, thermal injury (hypo/hyperthermia) or rhabdomyolysis.
- In TTP, the coagulation and D-dimers are usually normal: this can be used to differentiate TTP from DIC.

Coagulation abnormalities seen in DIC:

- APTT - elevated
- PT - elevated
- FDPs - elevated
- D-dimers - elevated
- Platelets - reduced
- Fibrinogen - reduced
- Protein C - reduced
- Antithrombin - reduced.

The diagnosis of DIC should encompass both laboratory and clinical findings

In 2009 the British Committee for Standards in Haematology (BCSH) released guidelines relating to the diagnosis and management of disseminated intravascular coagulation (DIC).

The cornerstone of the treatment of DIC is treatment of the underlying condition.

Transfusion of platelets or plasma components in patients with DIC should not be primarily based on laboratory results and should in general be reserved for patients who present with bleeding.

High D-Dimer & FDP is diagnostic

Haemophilia

- Haemophilia is **X-linked recessive** disorder of coagulation.
- Up to 30% of patients have no family history of the condition.

A) Haemophilia A

- ✗ It is due to a deficiency of **factor VIII**
- ✗ accounts for **90% of cases of haemophilia**

B) haemophilia B (Christmas disease) there is a **lack of factor IX**

Features:

- 1) haemarthroses, haematomas
- 2) prolonged bleeding after surgery or trauma

Blood tests:

- 1) **prolonged APTT**
 - 2) **bleeding time, thrombin time, prothrombin time normal**
 - 3) Up to 10-15% of patients with haemophilia A develop **antibodies to factor VIII** treatment
- A normal factor VIIIc activity points to a diagnosis of haemophilia B (lack of factor IX).

Acquired haemophilia (rare)

- Acquired Factor VIII inhibitor: **acquired allo-antibodies to factor VIII** (rarely factor IX);
- It can occur with **underlying malignancy** and **autoimmune conditions**.
- Bruising but with no or little joint bleeds.

MANAGEMENT revolves around activated factor VII, with factor VIII not being efficacious.

- 1) **Factor eight inhibitor bypassing agent** (FEIBA)
 - ✗ a commercially available agent used in those with inhibitors
 - ✗ has a mix of several other **ACTIVATED** clotting factors which bypass the factor VIII requiring step in the coagulation pathway
- 2) recombinant factor VII (NovoSeven)
- 3) Long term the inhibitor itself can be eradicated using immunosuppressants such as **cyclophosphamide** and **corticosteroids**.

A grossly elevated APTT may be caused by:

- 1) heparin therapy,
- 2) haemophilia or
- 3) Antiphospholipid syndrome.

Von Willebrand's disease

- The most common **inherited bleeding** disorder.
- The majority of cases are inherited in an **autosomal dominant** fashion
- characteristically behaves like a platelet disorder i.e:
 - ⇒ **epistaxis** and **menorrhagia** are common whilst
 - ⇒ haemarthroses and muscle haematomas are rare

Role of von Willebrand factor:

- large glycoprotein which forms massive multimers up to 1,000,000 Da in size
- promotes platelet adhesion to damaged endothelium
- carrier molecule for factor VIII

Types:

Type 1: partial reduction in vWF (**80%** of patients)

Type 2: abnormal form of vWF

Type 3: total lack of vWF (**most severe form**) **autosomal recessive**

Investigation:

- 1) **prolonged bleeding time**
- 2) **APTT** may be **prolonged**
- 3) factor VIII levels may be **moderately reduced**
- 4) **defective platelet aggregation** with ristocetin

Management:

- 1) **Tranexamic acid** (anti-fibrinolytic drug) for mild bleeding
 - 2) **Desmopressin (DDAVP)**: raises levels of vWF (3-5 fold) by inducing release of vWF from Weibel-Palade bodies in endothelial cells
 - 3) **vWB factor concentrate** would be reserved as second line treatment to DDAVP.
 - 4) **factor VIII concentrate**
- ☒ In minor trauma, desmopressin (DDAVP) can be used to increase the concentration of VWF.
- ☒ However for major surgery, factor VIII concentrate is used to increase the concentration of vWF. The most commonly used is Humate-P.
- ☒ Purified or recombinant VIII are avoided since they contain only small concentrations of vWF

In cases of severe vWD or prior to major surgery, the product of choice is **intermediate purity** (vWF rich) **factor VIII**, which contains the highest concentration of vWF.

Thrombophilia

Causes:

Inherited

- A) activated protein C resistance (factor V Leiden)
- B) protein C deficiency
- C) protein S deficiency
- D) Antithrombin III deficiency

Acquired:

- A) antiphospholipid syndrome
- B) the Pill

A) Activated protein C resistance: (factor V Leiden)

- The most common inherited thrombophilia.
- It is due to Factor V Leiden mutation.
Heterozygotes have a 5-fold risk of venous thrombosis whilst
Homozygotes have a 50-fold increased risk

B) Protein C deficiency:

An **autosomal codominant condition** which causes an increased risk of thrombosis

Features:

- 1) **venous thromboembolism**
- 2) **skin necrosis** following the commencement of warfarin:
 - ☒ When warfarin is first started biosynthesis of protein C is reduced.
 - ☒ This results in a temporary procoagulant state after initially starting warfarin,
 - ☒ Normally avoided by concurrent heparin administration.
 - ☒ Thrombosis may occur in venules leading to skin necrosis

C) Antithrombin III deficiency:

- **autosomal dominant**
- An inherited cause of thrombophilia occurring in approximately 1:2,000 of the population.
- Antithrombin III inhibits several clotting factors, primarily thrombin, factor X and factor IX. It mediates the effects of heparin
- Antithrombin III deficiency comprises a heterogeneous group of disorders:
 - 1) some patients having a deficiency of normal antithrombin III whilst
 - 2) others produce abnormal antithrombin III

Features:

- 1) recurrent venous thromboses
- 2) arterial thromboses do occur but is uncommon

Management:

- 1) Thromboembolic events are treated with **lifelong warfarinisation**
 - 2) **Heparinisation** during pregnancy*
 - 3) **Antithrombin III concentrates** (often used during surgery or childbirth)
- *as patients with antithrombin III deficiency have a degree of resistance to heparin anti-Xa levels should be monitored carefully to ensure adequate anticoagulation

Antiphospholipid syndrome

- An acquired disorder
- **Characterised by:**
 - 1) A predisposition to both venous and arterial thromboses,
 - 2) recurrent fetal loss and
 - 3) Thrombocytopenia, prolonged PTT.
 - 4) False positive VDRL.
- It may occur as a primary disorder or secondary to other conditions, most commonly SLE.

In pregnancy the following complications may occur:

- 1) recurrent miscarriage
- 2) IUGR
- 3) pre-eclampsia
- 4) placental abruption
- 5) pre-term delivery
- 6) venous thromboembolism

Management:

- 1) **low-dose aspirin** should be commenced **once the pregnancy is confirmed** on urine testing
 - 2) **Low molecular weight heparin:**
 - ⇒ Started once a **fetal heart** is seen on ultrasound.
 - ⇒ discontinued at **34 weeks** gestation
- These interventions increase the live birth rate 7-fold

Only lupus anticoagulant prolonged APTT that does not correct when mixed with normal plasma.

Thrombophilia screen testing

Considered useful in patients presenting with:

- 1) A first episode of venous thromboembolism (VTE) at a **young** age (less than 45 years of age)
- 2) **Idiopathic** venous thrombosis
- 3) **FH** of thrombosis, particularly in a first degree relative
- 4) VTE in an unusual vascular territory
- 5) Neonatal purpura fulminans
- 6) Warfarin induced skin necrosis

Venous thromboembolism

Risk factors:

Common predisposing factors include:

- 1) malignancy,
- 2) pregnancy and
- 3) the period following an operation

The greatest RISK factor for **recurrence of a venous thromboembolism (VTE)** is a **previous episode**.

The comprehensive list below is partly based on the 2010 SIGN venous thromboembolism (VTE) guidelines:

General Risk factors:

- 1) pregnancy (especially puerperium)
- 2) increased risk with advancing age
- 3) obesity
- 4) family history of VTE
- 5) immobility
- 6) hospitalisation
- 7) anaesthesia
- 8) central venous catheter: femoral >> subclavian

Underlying conditions:

- 1) malignancy
- 2) thrombophilia: e.g. Activated protein C resistance, protein C and S deficiency
- 3) antiphospholipid syndrome
- 4) heart failure
- 5) Behcet's
- 6) nephrotic syndrome
- 7) polycythaemia
- 8) sickle cell disease
- 9) paroxysmal nocturnal haemoglobinuria
- 10) hyperviscosity syndrome
- 11) homocystinuria

Medication:

- 1) COC pill: 3rd generation > than 2nd generation
- 2) HRT: the risk of VTE is higher in women taking oestrogen + progestogen preparations compared to those taking oestrogen only preparations
- 3) raloxifene and tamoxifen
- 4) Antipsychotics (especially **olanzapine**) have recently been shown to be a risk factor.

It should be remembered however that around 40% of patients diagnosed with a PE have no major risk factors.

Deep vein thrombosis

Diagnosis:

- NICE published guidelines in 2012 relating to the investigation and management of DVT.
- If a patient is suspected of having a DVT a two-level DVT Wells score should be performed:

Two-level DVT Wells score

Clinical feature	Points
Active cancer (treatment ongoing, within 6 months, or palliative)	1
Paralysis, paresis or recent plaster immobilisation of the lower extremities	1
• Recently bedridden for 3 days or more or • major surgery within 12 weeks requiring general or regional anaesthesia	1
Localised tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling at least 3 cm larger than asymptomatic side	1
Pitting oedema confined to the symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Previously documented DVT	1
An alternative diagnosis is at least as likely as DVT	-2

Clinical probability simplified score

- DVT likely: **2 points or more**
- DVT unlikely: **1 point or less**

A) If a DVT is 'likely' (2 points or more):

- ✓ a proximal leg vein ultrasound scan should be carried out within 4 hours and, if the result is negative, a D-dimer test
- ✓ if a proximal leg vein ultrasound scan cannot be carried out within 4 hours:
 - ⇒ a D-dimer test should be performed and
 - ⇒ LMWH administered whilst waiting for the proximal leg vein ultrasound scan (which should be performed within 24 hours)

B) If a DVT is 'unlikely' (1 point or less)

Perform a D-dimer test and if it is **positive** arrange:

- ✓ a proximal leg vein ultrasound scan within 4 hours
- ✓ if a proximal leg vein ultrasound scan cannot be carried out within 4 hours:
 - ⇒ LMWH should be administered whilst waiting for the proximal leg vein ultrasound scan (which should be performed within 24 hours)

Management:

Venous thromboembolism - length of warfarin treatment

- provoked (e.g. recent surgery): 3 months
 - unprovoked: 6 months
- 1) **Low molecular weight heparin** (LMWH) or **fondaparinux** should be given initially after a DVT is diagnosed.
 - 2) a vitamin K antagonist (i.e. **warfarin**) should be given within 24 hours of the diagnosis
 - 3) the **LMWH** or **fondaparinux** should be continued for at least **5 days** or until the international normalised ratio (**INR**) is **2.0** or above for at least 24 hours, whichever is longer, i.e. LMWH or fondaparinux is given at the same time as warfarin until the INR is in the therapeutic range
 - 4) **warfarin:**
 - ⇒ should be continued for at least 3 months.
 - ⇒ At 3 months, NICE advise that clinicians should 'assess the risks and benefits of extending treatment'
 - ⇒ NICE add 'consider extending warfarin beyond 3 months for patients with *unprovoked* proximal DVT if their risk of VTE recurrence is high and there is no additional risk of major bleeding'.
 - ⇒ This essentially means that if there was no obvious cause or provoking factor (surgery, trauma, significant immobility) it may imply the patient has a tendency to thrombosis and should be given treatment longer than the norm of 3 months.
 - ⇒ In practice most clinicians give 6 months of warfarin for patients with an unprovoked DVT/PE

Further investigations and thrombophilia screening

- As both malignancy and thrombophilia are obvious risk factors for DVT NICE make recommendations on how to investigate patients with unprovoked clots.

Investigations for cancer:

- 1) **a physical examination** (guided by the patient's full history) and
- 2) **Chest X-ray** and
- 3) **Blood tests** (CBC, S.Ca and LFTs) and urinalysis.
- 4) Consider further investigations for cancer with an **abdomino-pelvic CT scan** (and **mammogram** for women) in all patients > 40 years with a first unprovoked DVT or PE

Thrombophilia screening

- ✓ not offered if patients will be on lifelong warfarin (i.e. won't alter management)
- ✓ consider testing for antiphospholipid antibodies
- ✓ consider testing for hereditary thrombophilia in patients who have had unprovoked DVT or PE and who have a first-degree relative who has had DVT or PE

In 2010 The British Committee for Standards in Haematology (BCSH) released guidelines concerning travel-related venous thrombosis.

- Global use of compression stockings and anticoagulants for long distance travel is not indicated.
- Assessment of risk should be made on an individual basis but is likely that recent major surgery, active malignancy, previous unprovoked VTE with no associated temporary risk factor or presence of more than one risk factor identifies those travellers at highest thrombosis risk.
- Those deemed high risk undertaking journeys of longer than three hours should wear well fitted below knee compression hosiery

Post-thrombotic syndrome

It is increasingly recognised that patients may develop complications following a DVT. Venous outflow obstruction and venous insufficiency result in chronic venous hypertension. The resulting clinical syndrome is known as post thrombotic syndrome. The following features may be seen:

- painful, heavy calves
- pruritus
- swelling
- varicose veins
- venous ulceration

Compression stockings should be offered to all patients with deep vein thrombosis to help reduce the risk of post-thrombotic syndrome.

NICE state the following:

Offer below-knee graduated compression stockings with an ankle pressure greater than 23 mmHg to patients with proximal DVT a week after diagnosis or when swelling is reduced sufficiently and if there are no contraindications, and:

- *advise patients to continue wearing the stockings for at least 2 years*
- *ensure that the stockings are replaced two or three times per year or according to the manufacturer's instructions*
- *advise patients that the stockings need to be worn only on the affected leg or legs.*

DVT/PE in Pregnancy

- pregnancy is a hypercoagulable state
- majority occur in last trimester

Pathophysiology:

- 1) increase in factors VII, VIII, X and fibrinogen
- 2) decrease in protein S
- 3) uterus presses on IVC causing venous stasis in legs

Management:

- 1) warfarin contraindicated ????
- 2) S/C LMWH preferred to IV heparin (less bleeding and thrombocytopenia)

Superior vena cava obstruction

- SVC obstruction is an oncological emergency caused by compression of the SVC.
- It is most commonly associated with **lung cancer**.

Features:

- 1) **dyspnoea** is the most common symptom
- 2) swelling of the face, neck and arms - conjunctival and periorbital oedema may be seen
- 3) visual disturbance
- 4) headache
- 5) pulseless **jugular venous distension**

Causes:

- 1) common malignancies: small cell lung cancer, lymphoma
- 2) other malignancies: metastatic seminoma, Kaposi's sarcoma, breast cancer
- 3) aortic aneurysm
- 4) mediastinal fibrosis
- 5) goiter
- 6) SVC thrombosis

Management:

- 1) general: dexamethasone, balloon venoplasty, stenting
- 2) small cell: chemotherapy + radiotherapy
- 3) non-small cell: radiotherapy

Heparin

- There are two main types of heparin - **unfractionated**, 'standard' heparin or **LMWH**.
- Heparins generally act by activating antithrombin III.
- Unfractionated heparin forms a complex which inhibits thrombin, factors Xa, IXa, XIa and XIIa.
- LMWH however only increases the action of antithrombin III on factor Xa

	Standard heparin	Low molecular weight heparin
Administration	Intravenous	Subcutaneous
Duration of action	Short	Long
Mechanism of action	• Activates antithrombin III. • Forms a complex that inhibits thrombin, factors Xa, IXa, XIa and XIIa	• Activates antithrombin III. • Forms a complex that inhibits factor Xa
Side-effects	1) Bleeding 2) HIT 3) Osteoporosis	1) Bleeding 2) Lower risk of HIT and osteoporosis with LMWH
Monitoring	Activated partial thromboplastin time (APTT)	Anti-Factor Xa (although routine monitoring is not required)
Notes	Useful in situations where there is a high risk of bleeding as anticoagulation can be terminated rapidly	Now standard in the management of venous thromboembolism treatment and prophylaxis and acute coronary syndromes

- Both unfractionated and LMWH can cause **hyperkalaemia**.
- This is thought to be caused by inhibition of **aldosterone secretion**.
- Heparin overdose may be reversed by **protamine sulphate**, although this only partially reverses the effect of LMWH.

Protamine Sulphate

- The major adverse event related to treatment with heparin is bleeding.
- If a patient on heparin develops a major bleed, further doses should be withheld and, depending on the severity of the bleeding, protamine sulphate should be considered.
- Protamine sulphate is the antidote for heparin.
- This reverses most, but not all, of the effects of LMWH.
- The dose of protamine sulphate given is dependent upon the dose of heparin administered and the time of administration.
 - ☒ If protamine is given within eight hours of the LMWH then a maximum neutralising dose is 1 mg protamine/100 units (or 1 mg) of LMWH given in the last dose.
 - ☒ If more than eight hours have passed since the dose of LMWH was given, administer 0.5 mg protamine per 100 units (or 1 mg) of LMWH given.
- Protamine is administered by slow IV infusion (over 10 minutes) to avoid a hypotensive reaction.
- Protamine requires a high level of caution when being prescribed and administered.

Warfarin

- Warfarin is an oral anticoagulant
- Inhibits the reduction of vitamin K to its active **hydroquinone** form, which in turn acts as a cofactor in the **carboxylation** of **clotting factor** II, VII, IX and X (mnemonic 1972) and **protein C**.

Indications:

- 1) venous thromboembolism: target INR = 2.5, if recurrent 3.5
 - 2) atrial fibrillation, target INR = 2.5
 - 3) Mechanical heart valves, target INR depends on the valve type and location. Mitral valves generally require a higher INR than aortic valves.
- Patients on warfarin are monitored using the INR (international normalised ratio), the ratio of the prothrombin time for the patient over the normal prothrombin time.
 - Warfarin has a long half-life and achieving a stable INR may take several days.
 - There a variety of loading regimes and computer software is now often used to alter the dose.

Factors that may **potentiate** warfarin:

- 1) liver disease
- 2) P450 enzyme inhibitors, e.g.: **amiodarone**, **ciprofloxacin**
- 3) co-trimoxazole
- 4) cranberry juice
- 5) drugs which displace warfarin from plasma albumin, e.g. NSAIDs
- 6) inhibit platelet function: NSAIDs

Side-effects:

- 1) haemorrhage
- 2) teratogenic, although can be used in breast-feeding mothers
- 3) Skin necrosis:
 - ⇒ when warfarin is first started biosynthesis of protein C is reduced.
 - ⇒ This results in a temporary procoagulant state after initially starting warfarin, normally avoided by concurrent heparin administration.
 - ⇒ Thrombosis may occur in venules leading to skin necrosis
- 4) purple toes

Warfarin overdose

- The following is based on the BNF guidelines, which in turn take into account the British Committee for Standards in Haematology (BCSH) guidelines.
- A 2005 update of the BCSH guidelines emphasised the preference of **prothrombin complex concentrate** over **FFP** in major bleeding.

Situation	Management
Major bleeding	1) Stop warfarin 2) Give intravenous vitamin K 5mg (phytomenadione) 3) 4factor-Prothrombin complex concentrate - if not available then FFP*
INR > 8.0 Minor bleeding	1) Stop warfarin 2) Give intravenous vitamin K 1-3mg 3) Repeat dose of vitamin K if INR still too high after 24 hours 4) Restart warfarin when INR < 5.0
INR > 8.0 No bleeding	1) Stop warfarin 2) Give vitamin K 1-5mg by mouth , using the intravenous preparation orally 3) Repeat dose of vitamin K if INR still too high after 24 hours 4) Restart when INR < 5.0
INR 5.0-8.0 Minor bleeding	1) Stop warfarin 2) Give intravenous vitamin K 1-3mg 3) Restart when INR < 5.0
INR 5.0-8.0 No bleeding	1) Withhold 1 or 2 doses of warfarin 2) Reduce subsequent maintenance dose

*as FFP can take time to defrost prothrombin complex concentrate should be considered in cases of intracranial haemorrhage

2008 BSG guidelines on the MANAGEMENT of anticoagulants at endoscopy

- ✗** Where the endoscopic procedure carries a high RISK of bleeding and the indication for anticoagulation is low risk for discontinuation then;
 - ⇒ anticoagulation should be discontinued until the INR is <1.5 and
 - ⇒ Restarted post-procedure.
 - ⇒ Bridging with heparin is not required.
- ✗** Bridging is only recommended if the indication for anticoagulation is high RISK - for example, mechanical mitral valve, atrial fibrillation (AF) and prosthetic valve, recent venous thromboembolism (VTE) (less than three months), thrombophilia.
- ✗** LMWH is relatively contraindicated in patients with an eGFR less than 30 mls/min, these patients may require admission for unfractionated heparin (UFH) infusion
- ✗** Where an endoscopic procedure is ASSOCIATED with a low risk of haemorrhage then the BSG recommends continuation of anticoagulation at the current dosage providing an INR within the last seven days is within the therapeutic range.

In 2011 the British Committee for Standards in Haematology (BCSH) released updated guidelines relating to warfarin use

- ✗** Patients who should be considered for bridging therapy:
 - 1) a VTE within the previous three months,
 - 2) Patients with AF and previous stroke or TIA or multiple other risk factors, and
 - 3) Patients with a mitral valve replacement.
- ✗** The most appropriate bridging therapy in this case is low molecular weight heparin, with the last dose being given not less than 24 hours prior to the procedure, the warfarin having been discontinued five days prior to the procedure.
- ✗** If the INR is still above 3 on the day prior to the procedure, vitamin K should be administered.

NB Aiming for a raised but sub-therapeutic INR is not recommended in any situation.

- Clopidogrel is ASSOCIATED with a much higher RISK of bleeding than aspirin.
- IHD without endovascular stents is considered a low risk condition for the temporary discontinuation of clopidogrel.
- Aspirin and clopidogrel are both irreversible inhibitors of platelet function and when they are to be discontinued must be stopped at least 7 days prior to procedure to significantly reduce the RISK of ASSOCIATED bleeding.

- Aspirin is not ASSOCIATED with the same degree of bleeding as clopidogrel and may be continued in those already taking it even prior to endoscopic intervention with a high risk of bleeding.
- In those not already prescribed aspirin it should be considered as a bridging AGENT if clopidogrel must be discontinued.
- Patients with coronary stents in place are at high risk of thrombosis if clopidogrel is discontinued. Their MANAGEMENT should be in conjunction with a cardiologist.
- The risk of thrombosis and thus stopping clopidogrel is reduced if more than 12 months have elapsed since insertion of a drug-eluting stent or more than one month after insertion of a bare-metal stent.

Hereditary haemorrhagic telangiectasia

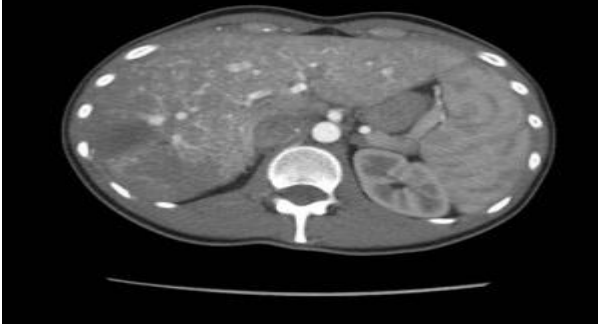
- Also known as **Osler-Weber-Rendu syndrome**,
- **Autosomal dominant** condition
- characterised by (as the name suggests) **multiple telangiectasia** over the skin and mucous membranes.
- 20% of cases occur spontaneously without prior family history.

There are 4 main diagnostic criteria:

- 1) epistaxis : spontaneous, recurrent nose bleeds
- 2) telangiectases: multiple at characteristic sites (lips, oral cavity, fingers, nose)
- 3) visceral lesions: for example
 - gastrointestinal telangiectasia (with or without bleeding),
 - pulmonary arteriovenous malformations (AVM),
 - hepatic AVM,
 - cerebral AVM,
 - spinal AVM
- 4) family history: a first-degree relative with HHT
 - If the patient has 2 then they are said to have a possible diagnosis of HHT.
 - If they meet 3 or more of the criteria they are said to have a definite diagnosis of HHT:



The chest x-ray shows multiple pulmonary nodules representing arteriovenous malformations, the largest in the right mid-zone.



The CT scan shows multiple hepatic arteriovenous malformations



Argon ablation is used for gastric antral vascular ectasia (GAVE).¹

Nasal skin grafts are used for persistent epistaxis

Oestrogen therapy can be effective especially in women but the evidence is not strong.

Common variable immunodeficiency (CVID)

- The most prevalent of the primary immunodeficiency diseases.
- The basic defect in CVID is a failure of B lymphocyte differentiation into plasma cells that produce the various immunoglobulin (Ig) subtypes.
- Patients with CVID often have marked reduction in serum levels of both IgG and IgA; approximately 50% of these patients also have reduced IgM.
- However, some patients have normal IgG levels but functional antibody deficiency may be present despite normal IgG subclass levels.
- The diagnosis is based on exclusion of known causes of defects of the humoral immune system.
- Most cases are sporadic, although familial cases exist that have various inheritance modes (including autosomal dominant with variable penetrance, autosomal recessive, and X linked).
- Regular intravenous immunoglobulin (IgG) infusions greatly reduce the frequency of recurrent respiratory tract infections.

Clinical manifestations of CVID include:

1) Recurrent infections:

- Principally recurrent **pyogenic** infections of upper and lower **respiratory tract**.
- This is the main clinical manifestation of CVID.
- Symptoms may appear during childhood or, more often, after adolescence.
- **Bronchiectasis** may develop if optimal therapy is delayed.
- *Haemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pneumoniae*, and *Staphylococcus aureus* are the organisms most commonly involved.
- Severe, recurrent infection with **herpes simplex** is also common.

2) Autoimmune diseases:

Patients may develop:

- Rheumatoid arthritis
- Haemolytic anemia
- Thrombocytopenia
- Neutropenia
- Thyroid abnormalities
- Vitiligo, and
- Keratoconjunctivitis sicca.
- About 20% of these patients have a **severe gastroenteropathy** with severe malabsorption resembling coeliac sprue, nodular lymphoid hyperplasia, and chronic inflammatory bowel disease such as ulcerative colitis and Crohn's disease.

A smaller number of patients develop:

- Achlorhydria and pernicious anemia
- Autoimmune hepatitis
- Primary biliary cirrhosis
- Alopecia totalis
- Hyperthyroidism
- Vasculitis, and
- Lymphoid interstitial pneumonia.

3) **Lymphoid hyperplasia and granulomatous diseases:**

- Atypical lymphoid hyperplasia due to clonal expansion of B or T lymphocytes has been reported in 1/3 of patients
- Granulomas have been reported in approximately 5-10% of patients with CVID.
- Granulomas are indistinguishable from those of classic sarcoidosis and are found in the:
 - ⇒ Lung
 - ⇒ Liver
 - ⇒ Spleen, and
 - ⇒ Conjunctivae.

4) **Predisposition to malignancy:**

- Patients with CVID have a high risk of developing malignant neoplasms (most commonly lymphoma, especially non-Hodgkin's lymphoma [NHL], and gastrointestinal [GI] carcinoma).
- Most lymphomas are of these are of the B cell immunophenotype and are frequently associated with Epstein-Barr virus (EBV).
- Lymphoma occurs 300 times more frequently in women with CVID than in affected men.

Other malignancies include:

- 1) Colon cancer
- 2) Breast cancer
- 3) Prostate cancer
- 4) Ovarian cancer
- 5) Oral cancer, and
- 6) Melanoma.

The diagnosis of cholesterol embolism should be considered in any patient with atherosclerotic disease presenting with deteriorating renal function, multisystem disease or distal ischaemia developing after an invasive arterial procedure.

The classic triad of presentation is:

- Eosinophilia
- Acute renal failure and
- Livedo reticularis.

Patients may also present with the features of an arterial embolus. Venous thrombosis is not a feature.

Conditions where plasmapheresis is considered the first line gold standard therapy include:

- 1) myasthenia gravis
- 2) Guillain-Barré syndrome
- 3) chronic inflammatory demyelinating polyneuropathy
- 4) hyperviscosity in monoclonal gammopathies
- 5) thrombotic thrombocytopenic purpura (using fresh frozen plasma)
- 6) Goodpasture syndrome (unless dialysis dependent and no diffuse alveolar hemorrhage)
- 7) haemolytic uremic syndrome (atypical form, due to autoantibody to factor H), and
- 8) fulminant Wilson disease.

In most conditions 5% albumin is the plasma substitute of choice (to reduce the risk of pathogen transmission), except for TTP where it has a therapeutic role in replacing the missing factor, ADAMTS-13.

a subconjunctival haemorrhage is an alarming adverse effect of aspirin therapy (and other antiplatelets).

It usually resolves over 10-14 days.

If the haematoma is large it may be worth considering prophylactic antibiotic eyedrops.

Metabolism of vincristine is inhibited by itraconazole causing increased risk of neurotoxicity which appears to be dose-related. The liver is the major excretory organ for vincristine in humans and animals.

Neurological toxicity manifested as peripheral or autonomic neuropathy is a feature of treatment with all vinca alkaloids and is a limiting side effect of vincristine.

If symptoms of neurotoxicity are severe, doses should be reduced. Generally recovery of the nervous system is very slow but in most cases complete.

The use of antifungals in haematology patients

- In patients who are prone to invasive fungal infections it is no longer suggested that empirical therapy with systemic antifungals is commenced (according to the latest British Committee for Standards in Haematology guidelines).
- Serological and/or imaging/biopsy should be sought prior to instituting antifungal therapy, but imaging would be the least invasive and most easily available modality of choice in order to investigate a suspected fungal infection.